SAGE Open Medical Case Reports
Volume 11: 1–5

DOI: 10.1177/2050313X231210390
journals.sagepub.com/home/sco
Sage

Cutaneous drug reaction secondary to antitubercular regimen: A case report from Nepal

Himal Bikram Bhattarai[1], Jeshika Yadav[2], Sangrila Sapkota[2], Adarsha Adhikari[1], Madhur Bhattarai[2], Ishani Singh[3], Sujan Shrestha[1], Jwala KC[4], Prakash Karki[5] and Bibhusan Basnet[6]

Abstract

Cutaneous adverse drug reactions are known side effects of first-line antitubercular therapy, which ranges from mild pruritus to life-threatening toxic epidermal necrolysis. Severe cutaneous adverse drug reactions can lead to antitubercular therapy discontinuation and further complicates tuberculosis treatment. Here we present the case of a 49-year-old obese male who developed a generalized maculopapular rash within 24 hours of initiation of therapy followed by bullae over palms in 3 days. Antitubercular therapy was immediately discontinued, and he was managed with antihistamines, intravenous fluid, and electrolyte supplementation. He was discharged on antihistamines, a short course of systemic steroids, moxifloxacin, and bedaquiline (second-line antitubercular therapy (ATT)). Proper guidelines about rechallenge therapy will enormously aid in managing cutaneous adverse drug reactions, and efficient treatment of tuberculosis in these patients, and ceasing its progression to multisystemic complications. This article aims to discuss the presentation and management of cutaneous adverse drug reactions in the setting of Nepal.

Keywords

Cutaneous adverse drug reactions, tuberculosis, anti-tubercular drug

Date received: 20 May 2023; accepted: 11 October 2023

Introduction

Tuberculosis (TB) is still considered to be one of the obstinate diseases, especially in developing countries like Nepal. It is estimated that around a quarter of the world's population has been infected with TB.[1] In Nepal, 27,745 TB cases were notified and registered at National Tuberculosis Program in the year 2020–21 (July 2020–July 2021).[1] Pulmonary TB is the most common manifestation of TB disease. First-line treatment with isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) remains the mainstay of treatment of TB, which has the adverse effects like hepatotoxicity, peripheral neuropathy, optic neuritis, and so on.[2–4]

Cutaneous Adverse Drug reactions (CADRs) are the well-known side effects of first-line antitubercular drugs; mild transient reactions (such as mild pruritus) do not result in treatment interruption. However, in severe cases, they can lead to life-threatening toxic epidermal necrolysis (TEN), which may necessitate to discontinuation of treatment and further complicate the treatment process.[5] Still, little emphasis is given to identification and management of CADRs. In a country like Nepal, where the TB burden is still a strenuous task to cope with, case reports about CADRs can provide a basic framework for managing the CADRs and efficient treatment of TB disease in these patients. More than one-fifth of patients with drug-induced skin necrosis develop fixed drug eruption (FDE), a common cutaneous medication reaction.[6] A FDE is not an uncommon adverse effect associated with over 100 different drugs. It is a recurrence at the

[1]Gandaki Medical College Teaching Hospital and Research Center, Pokhara, Nepal
[2]Institute of Medicine, Tribhuvan University, Kathmandu, Nepal
[3]Kathmandu Medical College Teaching Hospital, Kathmandu, Nepal
[4]Nobel Medical College Teaching Hospital, Biratnagar, Nepal
[5]Green Pastures Hospital, Pokhara, Nepal
[6]B.P. Koirala Institute of Health Science, Dharan, Nepal

Corresponding Author:
Madhur Bhattarai, Institute of Medicine, Tribhuvan University, Maharajgunj, Kathmandu 44600, Nepal.
Email: madhurbhattarai180@gmail.com

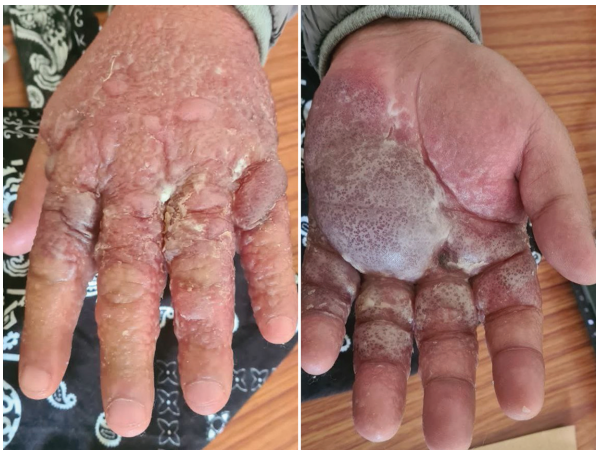

Figure 1. After beginning first-line antitubercular therapy.

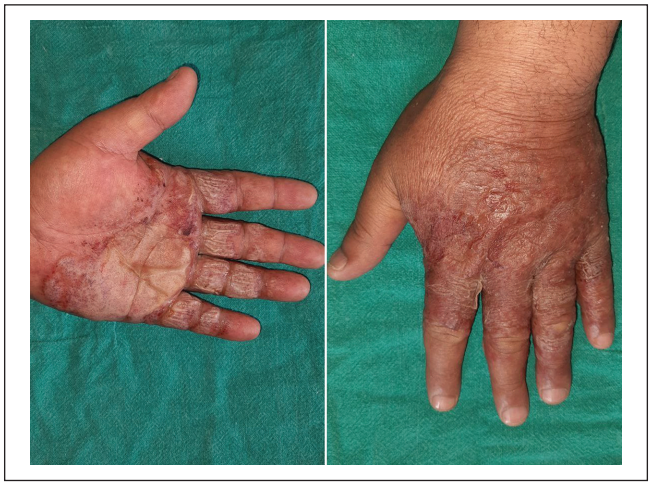

Figure 2. After treatment.

same site triggered by exposure to a certain drug. All FDEs are generally treated by locating and removing the underlying cause, typically accomplished by reviewing the patient's medical history, additional chemical exposures, and perhaps previous occurrences.[6]

Thus, we report the case of a 49-year-old male from Nepal with newly diagnosed pulmonary TB, who developed a cutaneous drug reaction while on antitubercular treatment. This article discusses the presentation of CADRs in the patient and the management strategies undertaken in Nepal's setting. This article is in line with CARE reporting checklist.[7]

Case presentation

A 49-year-old obese (93 kg) male from Western Nepal with newly diagnosed pulmonary tuberculosis (TB) on isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) (HRZE for 2 months and HR for 4 months is guideline for tb treatment) presented to the hospital with diffuse skin eruption for 3 days. The patient developed a pruritic rash on his left palm with flushing and rashes all over the body within 24 h of treatment initiation. Three days later, vesicular-bullous lesions appeared on the palmar and dorsal aspect of his hand, along with blanching and erythematous maculopapular rash on the upper extremities, abdomen, buttocks, dorsum, and palms, with bullae formation (Figure 1). No conjunctival involvement was observed during systemic examination. The patient has a medical history of type II diabetes mellitus (under Tab linagliptin 5 mg once daily) for 4months and hypertension (under Tab telmisartan 80 + 12.5 mg once daily and Tab amlodipine 5 mg once daily) for 5years. He has been a smoker for 4 years and is nonalcoholic. He had no known allergies to medications or other substances.

At a presentation to the hospital, he had blood pressure, oxygen saturation, and a heart rate of 130/100 mm of Hg, 97% under room air, and 74 beats/min, respectively. Laboratory examination showed normal hemoglobin, leukocyte count, and platelet levels, but increased eosinophils. He had elevated liver enzymes (serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase), but other parameters were within the normal range Table 1. Electrocardiogram showed a normal rhythm.

Due to the suspected allergic reaction, the standard antitubercular regimen was immediately discontinued. The patient was treated with antihistamines, intravenous fluid, and electrolyte supplementation, leading to symptom improvement. Following recovery, he was discharged on levocetirizine 10 mg for 1 week, prednisolone 30 mg once daily for 1 week, and calamine lotion as per the dermatologist's advice. He was also started on second-line ATT, including moxifloxacin 400 mg twice daily and bedaquiline 400 mg once daily. During follow-up after a week, there was a regression of rashes, and no new rashes were observed (Figure 2). Hence, the steroid therapy was gradually tapered over the next 10 days. On follow-up after 10 days, there was marked regression of rashes and the patient was remarkably improving.

Discussion

CADRs can vary in severity and presentation. Prompt recognition and appropriate management are essential to avoid treatment interruptions and potential complications. In this case, the patient's presentation of CADRs warranted immediate discontinuation of the standard antitubercular regimen. Supportive measures, including antihistamines and intravenous fluid, along with electrolyte supplementation, were effective in managing the allergic reaction. The patient was discharged on second-line ATT (moxifloxacin and bedaquiline) to continue TB treatment while minimizing the risk of adverse reactions. Follow-up assessments showed significant improvement, indicating successful management of the CADRs.

Table 1. Laboratory values of different lab parameters before and after treatment in a patient with CADRs to ATT.

Laboratory parameters	Before treatment	After treatment
Hemoglobin	14.3 gm/dl	14 gm/dl
Leukocyte count	10200 cells/mm^3	9300 cells/mm^3
Neutrophil	75%	68%
Lymphocyte	32%	34%
Eosinophils	9%	4%
Platelets	244000 cells/mm^3	253000 cells/mm^3
Prothrombin time	12 s	12 s
INR	0.9 s	0.9 s
Blood urea nitrogen	14 mg/dl	12 mg/dl
Creatinine	0.8 mg/dl	0.7 mg/dl
Blood sugar	110 mg/dl	122 mg/dl
Lactate dehydrogenase	109 mg/dl	96 mg/l
Sodium	140 mEq/l	140 mEq/l
Potassium	4.0 mEq/l	3.8 mEq/l
Erythrocyte sedimentation rate	8 mm/first hour	8 mm/first hour
C-reactive protein	5 mg/dl	3 mg/dl
Total bilirubin	0.8 mg/dl	0.8 mg/dl
Direct bilirubin	0.4 mg/dl	0.3 mg/dl
SGOT	104 U/l	86 U/l
SGPT	56 U/l	48 U/l

CADRs: cutaneous adverse drug reactions; ATT: antitubercular therapy; INR: international normalized ratio; SGOT: serum glutamic- oxaloacetic transaminase; SGPT: serum glutamic- pyruvic transaminase.

Naranjo Adverse Drug Reaction Probability score was used to assess the probability of CADR to ATT. This scoring system considers various factors such as the temporal relationship between drug administration and symptom onset, previous patient experience with the same drug, alternative explanations for the reaction, and the presence of evidence from laboratory tests. According to this system, a score of $\geqslant$9 is definitive, 5–8 is probable, 1–4 is possible, $\leqslant$0 is a doubtful case of adverse drug reaction. In our patient, there was no previous conclusive report on the adverse drug reactions; the adverse event appeared after the suspected drug was administered, which improved when the first-line antitubercular drug was discontinued. The first-line ATT was not readministered. Alternate causes, other than the drug was not known. There was no drug detected in the blood (or other fluids) in a concentration known to be toxic. The placebo effect was not elicited. The change in intensity of reactions after the change in dose of the drugs was not assessed. The patient did not have any previous exposure to first-line ATT. The adverse drug reaction was confirmed by objective evidence. Therefore, the Naranjo Adverse Drug Reaction Probability score is 4, which, according to the scoring system, is a possible case of an adverse drug reaction.[8]

The underlying pathogenesis of CADRs is complex and multifactorial, with the hapten theory being one of the possible mechanisms. The hapten theory suggests that drug metabolites, such as those of anti-TB drugs, can act as haptens and bind to skin proteins, triggering an immune response that leads to the development of CADRs. However, other factors, including the interplay between drugs, the immune system, and genetic factors, can also contribute to these reactions.[9]

Older adults, due to their medical conditions, use of multiple medications, and variations in drug absorption and liver metabolism, face a higher risk of developing CADRs. These reactions are less common in males because of certain hormonal factors, but our patient was an exception. While most patients develop a rash within 2months of treatment, our patient experienced CADRs within 3days of starting treatment.[5] The most frequently observed CADR with the treatment is a maculopapular rash, followed by other types like urticarial, lichenoid, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and exfoliative dermatitis.[5]

Our patient was undergoing first-line drug therapy when he developed a pruritic rash with multiple bullous formations and vesicular lesions on his left hand, both on the palmar and dorsal aspects. Suspecting an allergic reaction, the response was managed with antihistamines, intravenous fluid, electrolyte supplementation, and discontinuation of the anti-TB regimen. On follow-up after a week, there was an improvement with regression of rashes, and no new rashes were observed. Rechallenge was not yet started due to a lack of guidelines.[10] CADRs can vary in severity, and while there are no widely accepted grading systems, generally, mild reactions include simple rashes or itching, while moderate ones involve more extensive skin issues like blistering. Severe reactions, such as DRESS, Stevens Johnsons syndrome (SJS), toxic epidermal necrolysis (TEN), Drug hypersensitivity syndrome, cutaneous vasculitis, and FDEs, can be life-threatening and may necessitate hospitalization.[11] In our case, DRESS was unlikely as per the RegiSCAR scoring system to diagnose DRESS.[12] The treatment for CADRs depends on the severity of the reaction. Mild reactions can be managed with topical corticosteroids and antihistamines while continuing the anti-TB regimen under close clinical monitoring.[10] For moderate-to-severe cases, stopping the offending drug and using systemic corticosteroids or other immunosuppressive agents might be necessary to control the immune response. In severe or life-threatening situations, hospitalization and intravenous corticosteroids or immunosuppressive agents may be needed.[9] There has been growing interest in the usage of cyclosporine for treatment as a result of a surge in reports of serious generalized bullous fixed frug eruption (GBFDE) cases, including a study that revealed a substantial fatality rate in this illness.[13] A study in a pediatric patient with GBFDE was managed using 5 mg/kg cyclosporine subdivided into two daily dosages for a week, before receiving 2 weeks of 2.5 mg/kg/day.[14] Within 24 hours of commencing cyclosporine, this patient's erythema was reduced, and additional blistering stopped.[14] For GBFDE, no clinical studies have been conducted to

compare the efficacy of therapies such as topical steroid cream, a systemically administered steroid medication, or cyclosporine versus supportive care alone.[14]

Treatment interruption due to CADRs can have serious consequences for TB treatment. It can lead to drug resistance, treatment failure, and even increase the risk of mortality. The duration of the interruption also matters; longer interruptions tend to result in poorer outcomes compared to shorter ones, which are more manageable. Therefore, it is crucial to closely monitor and effectively manage CADRs in patients receiving anti-TB drugs. Each patient's situation is unique, so a personalized approach that considers the severity of the reaction and individual factors is essential to address these adverse events effectively. By doing so, we can strive for better treatment outcomes and ensure patients' well-being throughout their TB treatment journey.[9]

Rechallenge is the practice of resuming treatment with the same drug that caused the adverse drug reaction. It serves as a valuable tool to confirm the causative agent of the CADR. However, rechallenge comes with risks, as it may lead to the recurrence of adverse reactions and potentially more severe outcomes. Therefore, it should only be considered in specific situations where the causative agent is uncertain, and a thorough assessment of the risks and benefits is essential. If rechallenging is pursued, it should be conducted under close supervision and monitoring to detect any recurrence of the adverse reaction promptly. The decision to rechallenge with the same drug should be made carefully and in consultation with a healthcare provider experienced in managing these types of reactions.[9]

Limitation

A biopsy was not performed in our case. A biopsy is recommended for individuals with an ambiguous diagnosis or systemic signs that involve malaise, fever, or arthralgias, as well as in the variants of mucosal FDE, widespread FDE, and GBFDE.[6] Rechallenge was not performed due to a lack of guidelines and the potential risk of lethal side effects to patients. Further research is essential for the improvement of understanding among the medical community regarding CADRs like FDE/GFDE. In addition, in-depth inquiry of history and very long follow-up to better understand the course and recurrence is of utmost importance in patients like ours, as well as, to see other associations of the disease and response to other drugs which was not fully carried out in this case.[15,16]

Conclusion

Antihistamines, intravenous fluid, a short course of systemic corticosteroid, and electrolyte supplementation were used to manage CADRs in this patient. Identifying and reinstating alternative regimens in cases of adverse drug reaction (ADR) should be discussed with the patients, and the doctor should be highly suspicious if one occurs. We hope this case study will contribute to a broader understanding of probable CADRs causative agents and their interactions with different people in various settings.

Acknowledgements

The authors do not have any acknowledgment to report for this article.

Author contributions

H.B.B., J.Y., and S.S. wrote, reviewed, and edited the original article. A.A., M.B., I.S., S.S., J.K., P.K., and B.B. reviewed and edited the original article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for his anonymized information to be published in this article.

ORCID iDs

Adarsha Adhikari https://orcid.org/0000-0001-7261-478X
Madhur Bhattarai https://orcid.org/0000-0001-6382-1082
Ishani Singh https://orcid.org/0000-0001-9327-4980

References

1. Department of Health Services. DOHS Annual Report (FY-2076/77) [Internet]. Ministry of Health and Population, Government of Nepal; p. 473 (accessed 27 July 2023). https://dohs.gov.np/wp-content/uploads/2021/07/DoHS-Annual-Report-FY-2076-77-for-website.pdf
2. Shah S, Adhikari YR, Paudel S, et al. Optic neuropathy induced by ethambutol: a rare case from Nepal. *Ann Med Surg (Lond)* 2022; 77: 103637.
3. National Tuberculosis Centre. National Tuberculosis Management Guidelines [Internet]. Ministry of Health and Population, Government of Nepal; p. 152 (2019, accessed 22 April 2023). https://nepalntp.gov.np/wp-content/uploads/2019/10/National-Tuberculosis-Management-Guidelines-2019_Nepal.pdf
4. Pant P, Joshi A, Adhikari YR, et al. Pattern of tuberculosis, trend and outcome of patients registered at DOTS centre of a tertiary care hospital. *J Nepal Health Res Counc* 2022; 20(1): 54–58.
5. Sharma RK, Verma GK, Tegta GR, et al. Spectrum of cutaneous adverse drug reactions to anti-tubercular drugs and safe therapy after re-challenge – a retrospective study. *Indian Dermatol Online J* 2020; 11(2): 177–181.

6. Patel S, John AM, Handler MZ, et al. Fixed drug eruptions: an update, emphasizing the potentially lethal generalized bullous fixed drug eruption. *Am J Clin Dermatol* 2020; 21(3): 393–399.
7. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: explanation and elaboration document. *J Clin Epidemiol* 2017; 89: 218–235.
8. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239–245
9. Lehloenya RJ and 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): 475–486.
10. Tan JL, Nordin S and Besari AM. Rare clinical presentation of tuberculous meningitis: a case report. *Malays J Med Sci* 2017; 24(5): 119–123.
11. Adhikari YR, Bhattarai M, Baral B, et al. Drug reaction with eosinophilia and systemic symptoms syndrome secondary to isoniazid and ethambutol: a case report and literature review. *Ann Med Surg (Lond)* 2023; 85(5): 2180–2185.
12. Chen YC, Chang CY, Cho YT, et al. Reply to: "Using a diagnostic score when reporting the long-term sequelae of the drug reaction with eosinophilia and systemic symptoms." *J Am Acad Dermatol* 2013; 69(6): 1060–1062.
13. Lipowicz S, Sekula P, Ingen-Housz-Oro S, et al. Prognosis of generalized bullous fixed drug eruption: comparison with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 2013; 168(4): 726–732.
14. Barootes HC, Peebles ER, Matsui D, et al. Severe generalized bullous fixed drug eruption treated with cyclosporine: a case report and literature review. *Case Rep Dermatol* 2021; 13(1): 154–163.
15. Zawar V, Kirloskar M and Chuh A. Fixed drug eruption – a sexually inducible reaction? *Int J STD AIDS* 2004; 15(8): 560–563.
16. Kauppinen K and Stubb S. Fixed eruptions: causative drugs and challenge tests. *Br J Dermatol* 1985; 112(5): 575–578.