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Article

A Burning Paradox: Erythema Multiforme Induced by First Line Antitubercular Therapy-A Rare Case Report

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Abstract: Skin involvement in tuberculosis may result from the disease or its therapy. Dermatological manifestations range from pruritus, urticaria, angioedema, and fixed drug eruptions to erythema multiforme (EM), Stevens–Johnson syndrome, and toxic epidermal necrolysis (TEN) [3–5]. EM is an acute inflammatory hypersensitivity reaction with maculopapular and bullous lesions, often drug-induced [3,4]. Although rare, isoniazid, rifampicin, and ethambutol have been implicated in EM and TEN, with severe reactions carrying mortality rates up to 40% [5–7]. Here, we report a rare case of EM induced by first-line anti-TB therapy.

Keywords: Erythema Multiforme (EM), Tuberculosis (TB), Anti-TB Therapy, Hypersensitivity Reaction, Isoniazid, Rifampicin, Ethambutol.

INTRODUCTION

A burning paradox in tuberculosis management is that the very drugs designed to cure can also trigger rare, severe cutaneous reactions. First-line anti-tuberculous (anti-TB) therapy with rifampicin, isoniazid, pyrazinamide, and ethambutol/streptomycin is highly effective; however, major adverse drug reactions (ADRs) may necessitate discontinuation, complicating treatment and contributing to morbidity and mortality [1,2]. Cutaneous adverse drug reactions (CADRs), defined as skin reactions secondary to systemic drug administration, are among the most frequent ADRs to anti-TB drugs, with skin rashes being the second most common and a significant treatment barrier [1,2].

Skin involvement in tuberculosis may result from the disease or its therapy. Dermatological manifestations range from pruritus, urticaria, angioedema, and fixed drug eruptions to erythema multiforme (EM), Stevens–Johnson syndrome, and toxic epidermal necrolysis (TEN) [3–5]. EM is an acute inflammatory hypersensitivity reaction with maculopapular and bullous lesions, often drug-induced [3,4]. Although rare, isoniazid, rifampicin, and ethambutol have been implicated in EM and TEN, with severe reactions carrying mortality rates up to 40% [5–7]. Here, we report a rare case of EM induced by first-line anti-TB therapy.

CASE REPORT

A 25-year-old female from low socioeconomic status, weighing 42 kg, presented with complaints of persistent cough and evening rise of temperature for two weeks. She initially consulted an ASHA worker, who referred her to a Primary Health Centre (PHC), where sputum smear for acid-fast bacillus (AFB) tested positive and chest X-ray revealed findings consistent with pulmonary tuberculosis. She was started on first-line anti-tubercular therapy (ATT) under the standard regimen. She was counselled to take medications regularly, avoid discontinuation, and report immediately in case of adverse reactions

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or persistent fever.

After three weeks of treatment, she developed acute onset, progressively worsening pruritic rashes associated with intermittent fever responding to medication. On examination, multiple polygonal scaly plaques with well-demarcated, thin, white, semi-adherent scales were observed in a reticular and geographic pattern over the entire body, predominantly on the extensor aspects of the lower limbs. Total leukocyte count was markedly raised at 30,300 cells/mm³, with neutrophils 83%, lymphocytes 7.3%, monocytes 8%, eosinophils 0.8%, and basophils 6.8. Blood urea nitrogen was 8 mg/dl, and HIV screening was negative. No history of exposure to environmental toxins, insect bites, or intercurrent infections was reported.

She was provisionally diagnosed as a case of drug-induced cutaneous adverse reaction, likely erythema multiforme (EM). ATT was withheld, and dermatology consultation was obtained. The patient was treated symptomatically with oral corticosteroids (prednisolone) and antihistamines, following which her general condition improved, and rashes gradually subsided.

On reintroduction of fixed-dose combination (4FDC) ATT, the patient again developed cutaneous lesions, leading to immediate discontinuation. Subsequently, individual first-line ATT drugs were reintroduced one by one with gradual dose escalation. Remarkably, the patient tolerated all four drugs when given separately, without recurrence of cutaneous reactions. She was thus continued on individual drug formulations rather than the fixed-dose combination. The patient is currently under regular follow-up and is showing progressive clinical improvement.

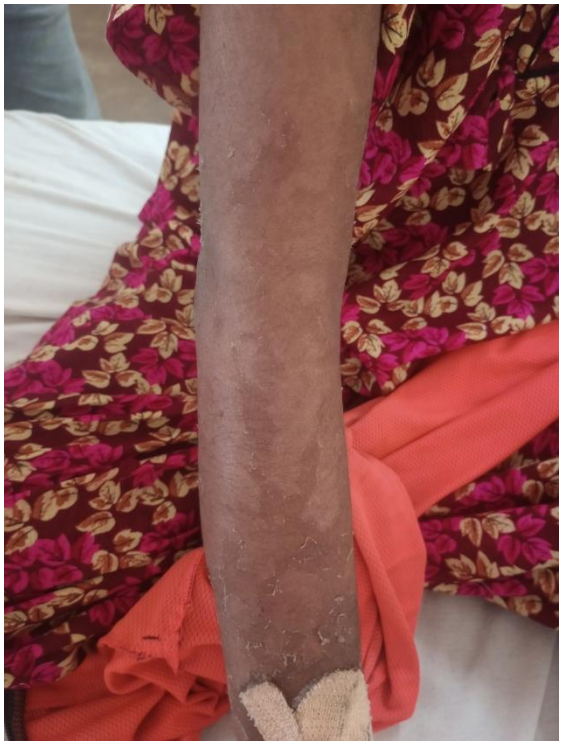

Figure 1: Diffuse erythematous, scaly lesions over the forearm, consistent with drug-induced cutaneous hypersensitivity.

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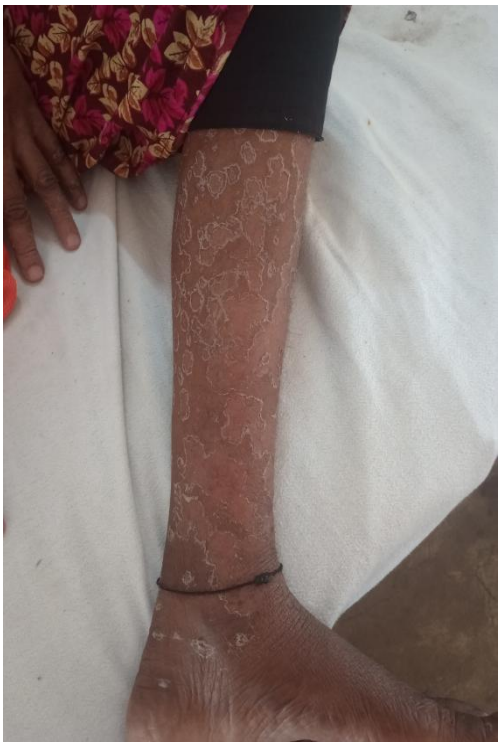

Figure 2: Xerotic and erythematous plaques involving the extensor surface of the arm, suggestive of erythema multiforme.

Figure 3: Facial involvement showing erythematous plaques with post-inflammatory hyperpigmentation.

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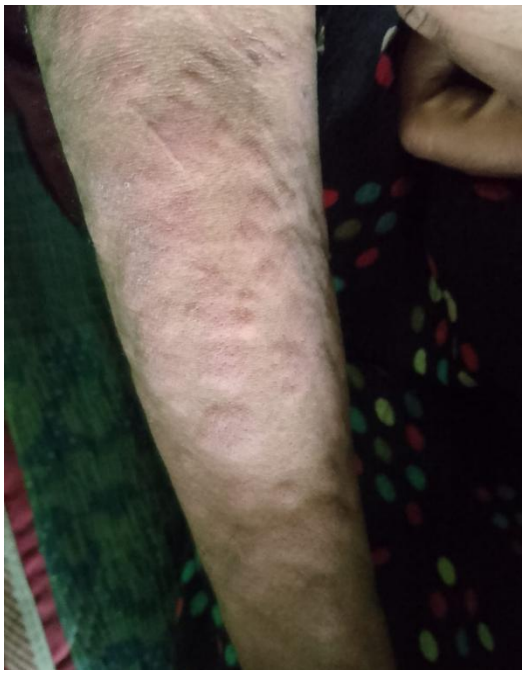

Figure 4: Irregular erythematous, scaly patches over the leg, indicating systemic distribution of erythema multiforme secondary to first-line antitubercular therapy.

Erythema multiforme (EM) is generally a self-limiting hypersensitivity reaction, often preceded by mild or no prodromal symptoms. It typically presents with numerous sharply demarcated red or pink macules and papules within 72 hours of exposure to a drug or infectious insult. These may evolve into plaques with central blistering or necrosis, forming the classic "target" or "iris" lesion, often accompanied by burning sensation and pruritus. Most cases resolve spontaneously within three to five weeks without sequelae [3,4]. Diagnosis is primarily clinical but may be confirmed by skin biopsy, which characteristically reveals eosinophilic and lymphocytic infiltration, vacuolar degeneration of the basal layer, and dermal perivascular lymphocytic infiltrates [4].

Globally, the incidence of EM is estimated at 1.2–6 cases per million individuals per year, with anti-tubercular drugs being among the notable triggers [5]. Although pyrazinamide-induced EM has been reported rarely [4,8], cases linked to isoniazid and rifampicin have also been documented [5–7]. In our case, the patient developed generalized scaly plaques after three weeks of initiating first-line ATT, later confirmed as EM. Interestingly, unlike the typical 72-hour onset described in the literature [3,4], our patient presented with delayed manifestations, suggesting that EM related to ATT may have a variable latency period.

Management of CADRs requires immediate withdrawal of the suspected drug and supportive therapy with corticosteroids and antihistamines [6]. In our case, withholding ATT and initiating prednisolone led to rapid improvement. A key diagnostic step was rechallenge testing: while reintroduction of 4FDC triggered recurrence of lesions, gradual reintroduction of individual first-line agents was well tolerated, allowing continuation of therapy. This aligns with recommendations that rechallenge and drug patch testing may aid in identifying the culprit drug in patients on multidrug regimens [9].

Immunologically, EM is considered a type IV hypersensitivity reaction mediated by CD8+ T lymphocytes, macrophages, and CD4+ lymphocytes infiltrating the dermis and epidermis. These immune cells release cytokines, causing epithelial apoptosis and the characteristic lesions [3,4]. Causality assessment using standard tools such as the WHO-UMC or Naranjo criteria classifies reactions confirmed by rechallenge as "certain" or "definite," strengthening the association between ATT and EM in this case [8].

This case highlights the paradoxical challenge in tuberculosis treatment: while first-line ATT is life-saving, it can rarely provoke severe CADRs like EM. Awareness of such adverse effects, timely diagnosis, and stepwise rechallenge protocols are essential to avoid unnecessary discontinuation of therapy and ensure treatment adherence. National pharmacovigilance initiatives, such as E-Nikshya under RNTCP in collaboration with PvPI, are vital for strengthening ADR reporting and physician awareness [8].

CONCLUSION

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Erythema multiforme is a rare but important cutaneous adverse reaction to first-line anti-tubercular therapy. Early recognition, prompt drug withdrawal, and supportive management are essential to prevent morbidity. Sequential rechallenge with individual drugs is a safe and effective strategy that allows continuation of life-saving therapy while minimizing adverse outcomes. Strengthening pharmacovigilance and physician awareness is crucial for timely identification and reporting of such rare events.

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