CASE REPORT

LEFLUNOMIDE INDUCED TOXIC EPIDERMOLYSIS NECROSIS IN PATIENT WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Leflunomide is immunomodulating agent used in rheumatoid arthritis and other rheumatic diseases like psoriatic arthritis and systemic lupus erythematous. Minor side effects of leflunomide (<10%) are rash, purpura but only severe case can lead to Steven johnson syndrome(SJS) or toxic epidermolysis. Causative agent (leflunomide) was discontinued and TEN was treated with methylprednisolone, cholestyramine and immunoglobulin. The skin lesion eventually resolved within 2-3 weeks with some hyperpigmentation.

Leflunomide is a drug that was used to prevent transplant rejection, however it's use has been diversified in treating in rheumatic diseases, psoriatic arthritis and SLE. Rheumatic diseases is autoimmune diseases that affects joints, tendon, muscle, ligaments, bones and muscles. We present the case of patient with rheumatic arthritis, who had been receiving leflunomide, prescribed by rheumatologist. The patient attends our hospital with picture of TEN after started using leflunomide

Key words: ***Leflunomide, Epidermolysis, Rheumatoid Arthritis***

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INTRODUCTION

Leflunomide is a disease-modifying anti rheumatic drug (DMARD) used in the treatment of rheumatoid arthritis and other autoimmune diseases. Despite its efficacy, leflunomide has been associated with severe adverse effects, including toxic epidermal necrolysis (TEN), a life-threatening dermatological condition characterized by widespread epidermal detachment and necrosis. TEN poses a significant challenge due to its high mortality rate and limited understanding of its pathophysiology and optimal management. This case reoprt aims to investigate the mechanisms underlying leflunomide-induced TEN and propose effective management strategies to mitigate its impact. Leflunomide is a prodrug that is quickly absorbed and converted into its active form. It inhibits enzyme tyrosine kinase, an enzyme key in translation of signals during cell formation and division, inhibiting production of pro inflammatory signals during cell formation and division, inhibiting pro inflammatory cytokines such as TNF-alpha and Il-17 and blocks TNF- mediated NF-Kb there by inhibiting activation of T cells.

A 55 year old male came to our hospital after referred from another government hospital of NEPAL (from Bir Hospital) for ICU intervention characterized by multiple skin lesion over face, back and B/L upper limb since 10 days. He also has redness and yellowish discharge in both eyes for 6 days. Also, patient complaints of unusual sensation over face with red raw oral lesion for 9 days. Patient is under leflunomide, tab HCQ, R/C seroflo, R/C Tiova. In addition to that, patient has other comorbid condition of DM, HTN and COPD.

On physical examination, patient was in a fair general condition, afebrile (BP= 130/90 mm/HG , RR 16).

With suspension of leflunomide and supportive measures during hospitalization for management of rheumatoid arthritis, 8 days later, he presents favourable evolution with clear improvement of cutaneous and mucosal lesions. The patient was discharged from our hospital with following medications.

Tab cortilone 40mg PO OD for 7days, then 20mg PO OD next 7days (8am)

tab hydroxyzine hydrochloride 25mg PO BD for 10days then PO HS 10 days.

Valomoist lotion LA (moisturing lotion) BD for 3 week

HISTORY OF PRESENTING ILLNESS

Abnormal sensation over face for 9 days

- Acute sensation over left side of face.
- No any history of loss of consciousness, seizure.

Skin rashes since 10 days

- Started on 4th day of new drug intake
- Multiple erythematous rash appears on face, back and bilateral upper limbs.
- Associated with burning sensation over wound sites making difficulty for patient to move.
- Color changes to dusk red and bluish discoloration over site
- Appearance of vesicular fluid filled lesion over both arms, back and face.
- Subsequent denudation of some of lesion leading to painful red raw areas.

Multiple painful red raw oral lesions for 9 days

- Started on 6th day of drug intake.
- It involved various inner and outer aspects of upper and lower lips, cheeks and lateral surface of tongue.
- Associated with bleeding from lesion on lips.
- Since then patient has difficult in eating and swallowing.

Ocular symptoms for 6 days

- Started on 6th day of drug intake.
- Complaint of redness and yellowish sticky discharge in both eyes.
- Associated with blurry vision

How to Cite

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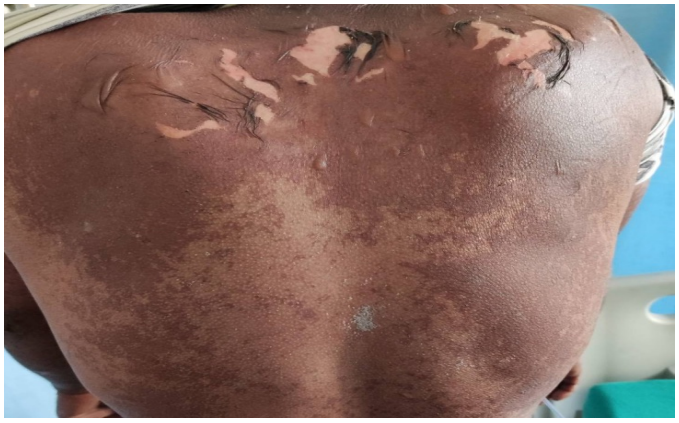
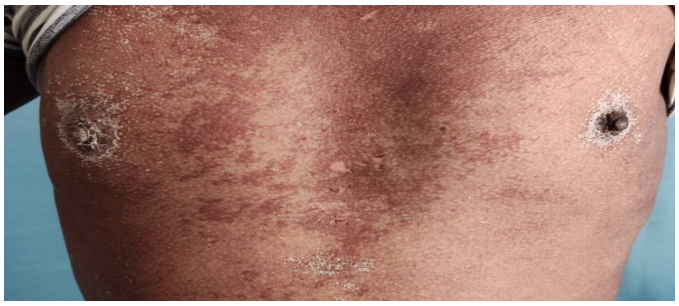
LOCAL EXAMINATION

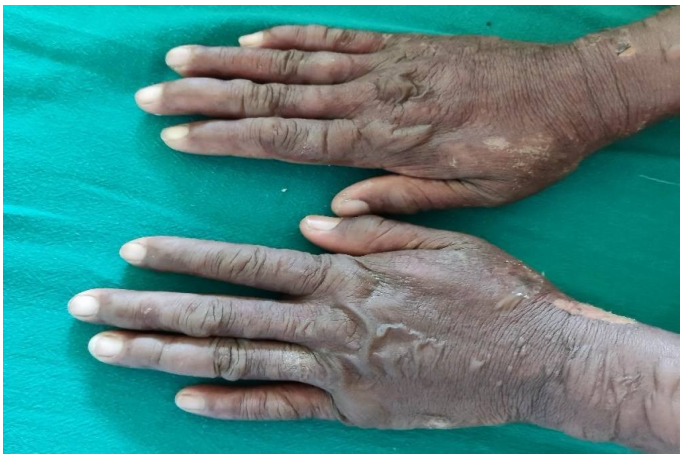
Skin findings

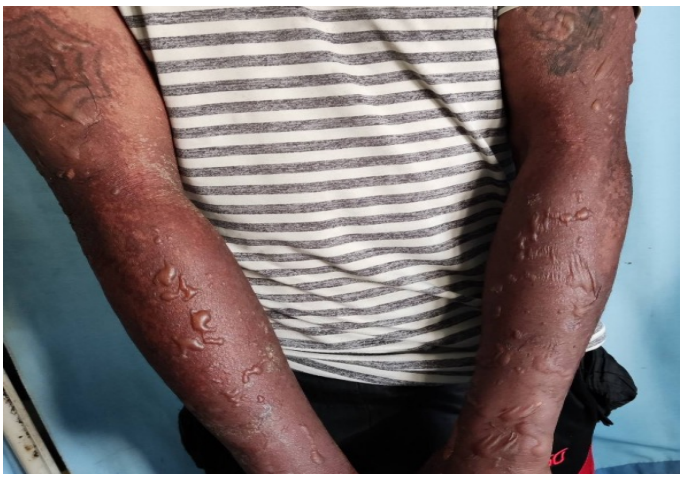
Various dusky red purpura with size 1mm to 1cm over chest, abdomen, back and bilateral upper arms





Vesicles and bullae



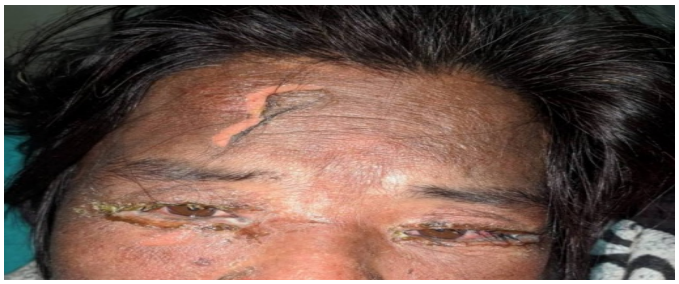


Flaccid, intact with size 3mm to 4cm with serous fluids

ORAL CAVITY EXAMINATION

- Multiple erosions over vermillion region of lips, labial mucosa with edematous lips.
- Hemorrhagic crust on vermillion region.
- Whitish slough on bilateral buccal mucosa.

OCULAR EXAMINATION



Purulent discharge, yellowish to brownish crust over upper and lower eyelids with matting of eyelashes.

POINTS IN FAVOUR

- Acute onset and rapid progression
- Correlation with leflunomide with latency of 4 days.
- Typical cutaneous lesion: dusky red to purplish vesicles, macule, epidermal detachment and positive nikolsky sign.
- Body surface area more than 30% and involvement of two mucosae.

SUPPORTIVE MANAGEMENT

- Fluid & electrolyte balance
- Maintenance of temperature: 25-28oC
- Wound care
- Frequent monitoring for progression to AKI, sepsis, ARDS, MODS or DIC
- Nutritional support
- Prevention & control of infection
- Pain management
- Ophthalmologic care
- Care of oral cavity

TREATMENT FOR SJS/TEN

Systemic corticosteroid

- Oral prednisolone 0.5–1 mg/kg daily for 10 days, and tapered; or IV methylprednisolone 500 mg on 3 consecutive days
- Hydrocortisone iv starting from high dose, rapidly tapered over 4-5 days

Adjunctives: Proton pump inhibitor

Other options:

- Cyclosporine (3mg/kg/day) for 10days
- TNF-alpha inhibitor (Etanercept 50mg sc single dose) IV Ig (2g/kg/day) over 3 days.

GENERAL PRINCIPLE OF MANAGEMENT

- Early recognition & immediate withdrawal of offending drug
- Investigations and rapid evaluation of severity and prognosis for admission in the most appropriate health care setting
- Multidisciplinary approach
- Appropriate supportive management
- Specific treatment

MANAGEMENT STRATEGIES

- Systematic review and meta-analysis of existing literature on the management of drug-induced TEN, with a focus on leflunomide-induced cases.
- Development of clinical guidelines and treatment algorithms for the prevention, early detection, and management of leflunomide-induced TEN based on available evidence and expert consensus.
- Prospective observational study to assess the implementation and effectiveness of the proposed management strategies in clinical practice.

SIGNIFICANCE AND IMPACT

- The findings of this study may inform clinical practice guidelines and contribute to the development of personalized therapeutic approaches for patients at risk of leflunomide-induced TEN
- Enhanced understanding of drug-induced skin toxicity mechanisms may facilitate the development of novel targeted therapies and preventive strategies for this serious adverse reaction.

CONCLUSIONS

Leflunomide can induced TEN and can be serious threat to patients. So rheumatologist should be precautious while prescribing leflunomide and patient should be monitored or follow up to see any changes although it's side effects is very rare.

Leflunomide-induced toxic epidermal necrolysis represents a rare but potentially fatal adverse reaction associated with leflunomide therapy. This research proposal aims to advance our understanding of the pathogenesis, risk factors, clinical presentation, and management of leflunomide-induced TEN through a comprehensive approach integrating mechanistic studies, clinical research, and evidence-based practice. By addressing these critical knowledge gaps, this research has the potential to improve patient outcomes and inform clinical decision-making in the management of this serious drug reaction.

RECOMMENDATIONS

Dermatologist and both rheumatologist should work in co-ordination if encountered such case. Offending agent like Leflunomide should be stopped and should focus on other anti-rheumatic drugs. Even though case like this are very rare but can pose serious threat to patient. No any clinician should ignore this fact.

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AUTHORS' CONTRIBUTION

Both authors conceived the study, developed proposal, research tool and conducted the study. The first author involved in report writing, case report finalization whereas the co-author involved in data editing, finalization of report and case report preparation.

COMPETING INTEREST

The authors declare no competing interest.