ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 02 | February - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# "ACECLOFENAC INDUCED TOXIC EPIDERMAL NECROLYSIS: CASE REPORT"

Medical Science

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## ABSTRACT

Toxic Epidermal Necrolysis is potentially life threatening cutaneous disorder usually induced by drugs. NSAIDs are one of the common groups implicated in Drug induced TEN. Aceclofenac is a relatively new NSAID exhibiting preferential cyclooxygenase-2 inhibition. It is widely used in management of musculoskeletal disorders. This report describes TEN induced by Aceclofenac in a 58 year old female who self-medicated herself with higher dose of aceclofenac for knee joint pain.

## KEYWORDS

Severe Cutaneous Adverse drug Reactions (SCAR), Aceclofenac, Non-steroidal anti-inflamm atory drugs (NSAIDs)

### BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) are very useful in management of pain and inflammation, thus constitute one of the widely used group of drugs in healthcare management.[1,2] Aceclofenac is relatively new NSAID that exhibits preferential Cyclooxygenase-2 inhibition and strong anti-inflammatory activity comparable to Diclofenac.[3]

Stevens-Johnsons Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are potentially life threatening skin disorders that are usually induced by drug. NSAIDs are one of the commonly implicated drug class in the causation of these severe cutaneous drug reactions.[4] But TEN with Aceclofenac is rarely reported and to the best of our knowledge, there are only two reports of aceclofenac induced TEN in literature; one from[5] and one from India[6].

Here we report a case Aceclofenac induced Toxic Epidermal Necrolysis in a 58 year old female.

### Case Report

A 58 year old female patient presented to dermatology OPD with chief complaints of

- rash over the entire body including her face and mouth since 6 days and
- peeling of skin over trunk, both upper limbs and lower limbs since 5 days.

On further eliciting the history, the patient mentioned that she had taken tablet Aceclofenac 200 mg SR, over the counter, 6 days back for complaint of bilateral knee joint pain from a local pharmacy near her home. On taking two tablets Aceclofenac 200 mg SR, she had an episode of fever which was sudden onset, progressively high grade associated with nausea, malaise and arthralgia which was relieved on giving Paracetamol 500 mg by the family members. She also noticed that she developed a rash over her both upper limbs along with the trunk. The rash subsequently progressed to her face including her oral mucosa & around her both eyes, both lower limbs and finally spread to the entire body. The next day, there was peeling of skin on the rashes at her face, around her both eyes, both upper limbs, trunk and both lower limbs. The relatives of the patient took the patient to a local private practitioner where the symptoms could not be controlled and lesions continued to progress. She was referred to dermatology OPD of a tertiary care hospital. There was no history of burn injury, diarrhoea, haematuria, photophobia or burning micturition. The patient has no history of similar complaints in the past. She is a known case of hypothyroidism since 12 years for which she is taking tablet levothyroxine 25 mcg once a day and hypertension since past 10 years for which she is taking amlodipine 5 mg once daily. The patient was fully vaccinated against Covid-19 and had taken second dose of Covishield 6 months back. The patient had regularly been taking over the counter diclofenac sodium for knee joint pain for the last 3 months, at a local pharmacy near her home. There is no history of similar complaints in the family.

General examination revealed normal rate of pulse, respiration, normal blood pressure and temperature with no pallor, icterus, cyanosis, clubbing or lymphadenopathy. No significant finding was noticed during systemic examination. Findings of Local/ Dermatological examination were as follows;

- presence of generalised purpuric macules on face, inside the mouth, on both upper limbs, the entire trunk and on both lower limbs
- presence of desquamation of skin over purpuric macules over both upper limbs, back, both heels and face causing superficial erosions
- presence of oral apthae
- lips showed superficial erosions with crusting
- crusting on bilateral periocular area
- bilateral conjunctivae showed erythema
- presence of erosions on vaginal mucosa
- scalp was spared

As per rule of 9, approximately 40% of body surface area was involved in desquamation.

Laboratory Investigations: Liver Function Tests, Random Blood Sugar, urine protein were within normal limits. Complete Blood Count revealed Haemoglobin at 8 g/dl while other parameters were within normal limits. There was an increase in serum urea and serum creatinine levels. [serum urea: 50 mg/dl; serum creatinine: 1.5 mg/dl] SCORTEN SCORE came out to be 3

- age>40 years,
- epidermal detachment>30%,
- blood urea> 28 mg/dl

A diagnosis of Toxic Epidermal Necrolysis secondary to Aceclofenac consumption was made on the basis of history and clinical examination.

The patient was treated with Intravenous fluids, multivitamins, corticosteroids, oral anti-fungals and liquid paraffin was applied locally on the lesions. Wound care was done on the lesions for 5 days. Normal saline soaks were applied on the lips. Antibiotic prophylaxis was given to prevent any further infection of lesions.

The patient was admitted for 7 days where there was marked improvement in her symptoms. The spread of the skin lesions was stopped, older skin lesions healed and there were no new lesions occurring.

WHO-UMC causality assessment[7] came out to be "Probable" category as there was;

- Positive temporal association between drug intake and occurrence

of skin lesions.
- No other pathological explanation of the skin lesions.
- Positive De-challenge test as the skin lesions stopped spreading after the withdrawal of the drug.
- Re-challenge was not done.

## DISCUSSION

Toxic Epidermal Necrolysis is a potentially life-threatening cutaneous disorder associated with extensive erythema, necrosis blistering and detachment of epidermis and mucous membranes.

Drugs are commonly implicated in causation of TEN . but infection, malignancy and vaccinations have been proposed as other etiological factors.[3]

The underlying pathophysiology of TEN is not completely understood. It is considered tom be cytotoxic T cell mediated Human Leukocyte Antigen dependent drug hypersensitivity. At least 200 drugs have been reported to be associated with SJS/TEN.

Drug can elicit cytotoxic T-cell response by several mechanisms; drug or drug metabolite may act as hapten or pro-hapten, may directly interact with HLA protein, may alter the specificity of HLA or may bind directly with T-cell receptor which can eventually lead to T-cell activation. Upon activation, stimulated cytotoxic CD-8$^{+}$ cells kill autologous target cells.

Extensive apoptosis, sloughing and necrosis in keratinocytes and mucosal cells is brought about by cascade release of cytokines or chemokines including perforin/granzyme, Fas-FasL, TNF-α and granulysin.[8]

Besides strong association of SJS/TEN with certain HLA alleles, genetic variation in drug metabolising enzymes and drug transporters that play important role in pharmacokinetics of drugs also appears to be involves in pathogenesis of SJS/TEN. Viral and bacterial infections, malignancies, vaccination too can interact complexly with immune system and increasethe risk of developing SJS/TEN.[8]

Acute complications of extensive exfoliation of skin (>30%) and mucous membranes include septicaemia, renal hypoperfusion, acute tubular necrosis, renal insufficiency and septic shock. Delayed complications due to scarring and stricture formation in gastrointestinal tract, urogenital, ocular tissues are also seen.[9]

Management recommended by expert group involves prompt withdrawal of culprit drug, meticulous supportive care and judicious and early use of corticosteroids with or without cyclosporine[10] the estimated mortality rate is 10-70% depending upon quality of case and rapidity with which treatment is initiated.[11]

TEN can occur in all age groups, the mean age in TEN induced by NSAIDs is more than in SJS (57.7 ± 3.6 v/s 4.8 ± 2.6 years).[12]

In general, female sex appears to be more vulnerable to TEN.[12] the most common group of NSAIDs involved in SCARs are reported to be Proprionic acid derivatives and Salicylic acid.[12]

The mean time to symptom onset is reported to be 12.1 ± 3.8 for TEN induced by NSAIDs.[12] The time of symptom onset in previous case report of aceclofenac induced TEN is around 24 hours after taking 100 mg tablet of Aceclofenac[6] but in our case report it is less than 24 hours.

Relatively rapid onset in our case could be due to inadvertent high dose ( 2 tablets of 200 mg) of Aceclofenac. It also suggests possibility of direct effect of high plasma concentration of the drug on the interaction between the drug and immune cells.

In previous case report, Aceclofenac induced TEN proved to be fatal[6] while in our case, the patient showed improvement and was discharged after 7 days.

## CONCLUSION

Drug induced Toxic Epidermal Necrolysis is potentially life threatening disorder. Early detection and prompt treatment is crucial for better outcome. Aceclofenac can induce Toxic Epidermal Necrolysis in susceptible individuals.

**Images**

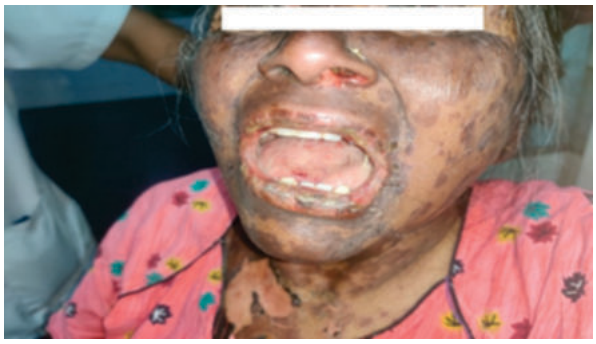

**Image 1. Lesions involving mouth & oral cavity**

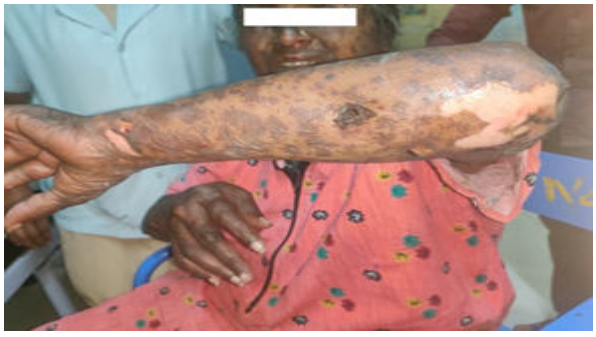

**Image 2. Lesions involving hands**

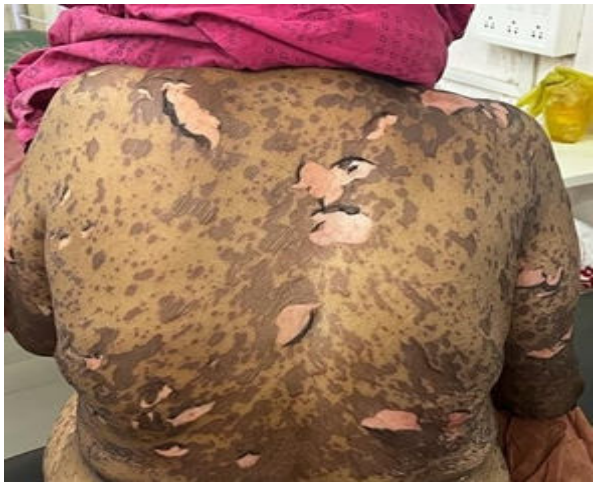

**Image 3. Lesions on the back**

**Key Message**

Aceclofenac is a relatively new NSAID with preferential COX-2 inhibiting activity and strong anti-inflammatory activity comparable to Diclofenac. Toxic Epidermal Necrolysis is a potentially life-threatening cutaneous disorder rarely reported with Aceclofenac.

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