When Severe Cutaneous Adverse Reactions Evolve: Drug Reaction with Eosinophilia and Systemic Symptoms Progressing to Toxic Epidermal Necrolysis in a Filipino Patient

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INTRODUCTION

Severe cutaneous adverse reactions (SCARs) are rare but life-threatening drug-induced hypersensitivity syndromes that include drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). These conditions carry high morbidity and mortality, with DRESS reported to have a mortality rate of up to 10% and TEN reaching 25–35%.[5,8] Although traditionally regarded as distinct entities, emerging evidence suggests that DRESS and TEN may represent different clinical expressions within a shared immunopathogenic spectrum, driven primarily by T-cell–mediated responses.[9]

A wide range of medications has been implicated in SCARs, most notably anticonvulsants, sulfonamides, antibiotics, and allopurinol.[10,13] More recently, non-classical culprit drugs such as fenofibrate and leflunomide have been identified as rare but important triggers.[4,14] Fenofibrate, in particular, has been linked to DRESS through case reports describing systemic involvement and histopathologic confirmation.[14] Early recognition and discontinuation of these atypical culprit agents are crucial to preventing progression and improving patient outcomes.

We report the case of a Filipino woman who developed DRESS, which progressed to TEN, most likely secondary to fenofibrate. This case contributes to the evolving understanding of SCAR overlap, highlights the diagnostic and therapeutic challenges, and underscores the importance of early recognition and prompt withdrawal of the offending drugs.

CASE PRESENTATION

A 50-year-old Filipino woman with a longstanding history of ankylosing spondylitis and type 2 diabetes mellitus, well-controlled with oral hypoglycemic agents, was admitted to our institution for evaluation of fever and morbilliform cutaneous lesions. Her medication history was notable for the initiation of leflunomide, fenofibrate, and semaglutide approximately two months prior to presentation. She denied any personal or family history of drug hypersensitivity or other known autoimmune disease, as well as any recent infectious illnesses.

Two weeks prior to admission, the patient developed undocumented fever, aphthous ulcers, chills, and sore throat. She self-medicated with paracetamol 500 mg/tablet, 1 tablet every 4 hours as needed for the fever, which resulted in temporary defervescence. No cutaneous lesions were observed during this period.

One week prior to admission, she noted the onset of multiple erythematous macules, papules, and patches on the lower back, which subsequently spread centrifugally to involve the face, chest, abdomen, and bilateral upper and lower extremities, with associated moderate pruritus graded 5/10 in severity. Fever, chills, and sore throat persisted, prompting consultation at the emergency department and subsequent admission under the Internal Medicine service.

On the fifth day of admission, the patient was referred to the Dermatology service for further evaluation, co-management of cutaneous findings, and consideration of a skin punch biopsy. At that time, she exhibited a resolving morbilliform erythematous eruption involving more than 50% of the body surface area. Oral aphthous ulcers were persistent, and no lymphadenopathy was appreciated. Laboratory evaluation revealed leukopenia and elevated liver enzymes, including transaminitis and

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hyperbilirubinemia, while renal function remained within normal limits. Based on the clinical features and medication history, the initial impression was Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with leflunomide identified as the most likely culprit medication and fenofibrate and semaglutide as less probable alternative causes. All outpatient medications were withheld by the main service as a precautionary measure.

At the time of dermatologic examination, the patient had a total RegiSCAR score of 2 (fever 0, lymphadenopathy 1, eosinophilia 1, skin involvement >50% body surface area 1, skin lesion suggesting DRESS -1, organ involvement 1, resolution ≥ 15 days -1), which indicated probable DRESS. Given that the cutaneous eruption was already resolving and systemic symptoms could not be reliably evaluated due to ongoing corticosteroid therapy (hydrocortisone 100 mg IV, Day 4), biopsy was deferred. Adjunctive therapy was initiated with clobetasol propionate 0.05% lotion, triamcinolone acetonide 0.1% lotion, and emollients. Supportive measures included normal saline irrigation and wound care. The patient's symptoms gradually improved, with resolution of fever and cutaneous lesions. She was subsequently discharged by the main service with the following medications paracetamol 500 mg/tablet, sitagliptin 100 mg/tablet, pregabalin + mecobalamin 75/75 mg/tab, nebivolol 5mg/tablet, fenofibrate 100 mg/tab, carbenoxolone 2% oral gel, chlorhexidine gargle, and clobetasol propionate 0.05% lotion. Close outpatient follow-up was advised.

Two days after discharge, the patient was re-admitted under the main service due to recurrence and progression of the previous cutaneous eruption. The lesions demonstrated increased erythema, size, and thickness, with widespread distribution over the face, trunk, back, and extremities. Crusting and fissuring of the lips were also noted, accompanied by recurrent undocumented fever, severe arthralgia (pain severity 10/10), and facial swelling. She was subsequently referred back to the dermatology service for further evaluation.

On physical examination, multiple, well-defined, non-blanching erythematous to violaceous, macules and papules were observed, some coalescing into patches and plaques with overlying scales, involving the face, neck, trunk, bilateral upper and lower extremities, including palms and soles. In addition, pustules on an erythematous base were present in the bilateral axilla (Figure 1). Facial edema (Figure 2) and cheilitis with crusting and scaling of the lips were documented, although no oral mucosal lesions were observed. Tender lymphadenopathy was appreciated in the bilateral posterior cervical, bilateral inguinal, and posterior popliteal areas. On re-admission, a second RegiSCAR assessment yielded a score of 4 (fever 0, lymphadenopathy 1, eosinophilia 1, skin involvement >50% body surface area 1, skin lesion suggesting DRESS 1, organ involvement 1, resolution ≥ 15 days -1), this corresponded to a probable case of DRESS, probably secondary to 1) fenofibrate 2) leflunomide and 3) semaglutide.

A 4mm punch biopsy was performed on an indurated papule on the left thigh (Figure 3). Histopathologic examination revealed an epidermis of normal thickness with overlying basketweave orthokeratosis. Focal vacuolar alteration with associated exocytosis of lymphocytes was observed at the dermoepidermal junction. In the dermis, a superficial perivascular and interstitial lymphocytic infiltrate was identified, accompanied by scattered interstitial eosinophils (Figure 3). These findings were signed out as Superficial Perivascular Dermatitis with Eosinophils, compatible with a diagnosis of DRESS.

The patient was managed with intravenous hydrocortisone (200 mg every 12 hours), clobetasol propionate 0.05% lotion, triamcinolone acetonide 0.1% lotion, and mupirocin 2% ointment. This regimen led to a marked decrease in erythema and scaling of previous lesions, with partial resolution into hyperpigmented patches, reduction in number of previous non-blanching lesions on the palms and dorsum of the feet, and decrease in facial swelling. However, residual scaling with minimal crusting of lip lesions persisted.

By the ninth day of admission, the patient was transitioned to oral prednisone (20 mg twice daily), with continued improvement of cutaneous lesions into hyperpigmented patches during subsequent days.

On the fourteenth day of admission, however, the patient developed recurrence of erythema and increase in scaling of prior lesions on the trunk, as well as yellowish crusting of lesions on the chest and back (Figure 4), associated with severe stinging pain (10/10) and skin fragility, characterized by detachment of the skin upon removal of clothing. Recurrent febrile episodes (maximum temperature: 39.1°C) accompanied by chills, odynophagia, dysphagia and dysgeusia were noted. In addition, new erythematous patches with erosions and overlying yellowish crusts developed on the medial upper eyelids, accompanied by mucoid discharge, along with increased crusting of previous lip lesions.

Additional findings included minimal facial swelling and whitish patches on the hard palate, without evidence of lymphadenopathy. Given the apparent clinical deterioration, there was a high index of suspicion for

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

The SCORTEN prognostic score was 3 (age >40 years, heart rate >120 bpm, and body surface area involvement >10%), corresponding to a predicted mortality rate of 35.8%. The working assessment was DRESS progressing to SJS/TEN overlap, most probably secondary to 1) leflunomide, 2) fenofibrate, and 3) semaglutide.

Drug causality was subsequently assessed using the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN), which identified Fenofibrate (score 7, very probable) as the most probable culprit. Leflunomide (score 4, probable) and Semaglutide (score 2, possible) were also considered, as all three agents had been initiated concurrently.

A 5-mm punch biopsy obtained from an eroded patch on the right forearm demonstrated full-thickness epidermal necrosis with confluent necrotic keratinocytes accompanied by neutrophils. Much of the upper epidermis was lost. Numerous neutrophils were arranged in a linear distribution at the base of the necrotic epidermis, with formation of an intraepidermal pustule. Prominent vacuolar interface changes were noted, while the dermis revealed only a sparse superficial perivascular lymphocytic infiltrate without eosinophils or additional neutrophils (Figure 5). The specimen was signed out as consistent with Stevens – Johnson Syndrome/ Toxic Epidermal Necrolysis Overlap.

The two biopsies highlight the histopathologic progression of the patient's condition. Initial biopsy revealed superficial perivascular dermatitis with eosinophils, consistent with DRESS. In contrast, the subsequent biopsy revealed full-thickness epidermal necrosis with intraepidermal pustule formation and sparse dermal inflammation without eosinophils - findings characteristic of SJS/TEN. Taken together, these sequential findings provide pathologic confirmation of clinical progression from DRESS to SJS/TEN overlap.

The patient was initiated on intravenous immunoglobulin at 30 g/day (0.4 g/kg/day) and empiric intravenous vancomycin 1 g every 12 hours. Despite these interventions, her condition deteriorated, and she developed septic shock leading to multiorgan failure, to which she ultimately succumbed.

CASE DISCUSSION

Etiology

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a life-threatening multiorgan adverse reaction that can be secondary to a myriad of drugs or by its metabolites. It is a hypersensitivity reaction often caused by anticonvulsants such as phenytoin, carbamazepine and phenobarbital, sulfa drugs and antibiotics such as penicillins.[1] Etiologic factors are unclear, however in a review of literature by De et. al, it stated its link with lymphocytic activation, drug metabolic enzyme defects, eosinophilia and human herpesvirus- 6 reactivation and Epstein-Barr virus.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe mucocutaneous disorders that represent a spectrum of the same disease process, primarily distinguished by the extent of epidermal detachment. These are strongly linked to drug exposure, with medications being recognized as the most critical precipitating factors. High-risk drugs commonly implicated include antibacterial sulfonamides, aromatic anticonvulsants (such as carbamazepine, phenytoin, and phenobarbital), allopurinol, oxicam nonsteroidal anti-inflammatory drugs, lamotrigine, and nevirapine.[11]

There is limited literature on SCAR overlap syndromes. Overlapping SCARs are defined as cases fulfilling the criteria for definite or probable diagnosis of at least 2 ADRs according to scoring systems. One study suggests that even if ambiguities among SCARs are not rare, confirmation of overlap cases are rare.[1]

Epidemiology

SCARs are rare and globally, there is an estimated 0.4-1.2 cases per million per year. Mortality rates range from 14%-70% SJS/TEN occurs in 1-2 cases per 1 million persons per year while DRESS occurs in 1 case per 10,000 medication exposures.[12]

In the Philippines, prevalence rates were estimated at 2.66–9.32/10,000 patients. However, this estimate is based on the Philippine Dermatological Society-Health Information System (PDS-HIS), with data coming from accredited dermatology training institutions which is not representative of the population.[12]

Pathophysiology

It is still not understood why certain individuals develop such severe immune response to medications and why effector cells are especially directed to the skin and other epithelia. Most literature indicates that drug specific T cell activation and genetic susceptibility are possible causes of this syndrome.[11]

DRESS and SJS-TEN are type IV hypersensitivity reactions which are T cell mediated, causing delayed hypersensitivity. Recent immunohistochemical and functional studies have demonstrated that distinct T-cell subsets and their effector functions contribute to the clinical variability observed among these SCARs. Specifically, drug-reactive T cells can recruit and activate various inflammatory cells such as monocytes, eosinophils, and neutrophils, and orchestrate cutaneous inflammation through the secretion of cytokines and chemokines. Granulysin has been identified as the principal cytokine inducing epidermal destruction in SJS-TEN. In contrast, eotaxin and interleukin-5 (IL-5) are associated with the eosinophilic inflammation observed in DRESS. To further explain the heterogeneity of these reactions, there was a proposed subclassification of Type IV hypersensitivity reactions based on cytokine profiles and effector cell recruitment. These include Type IVa (monocyte-dominant), Type IVb (eosinophil-dominant), and Type IVD (neutrophil-dominant) reactions.[1]

Histopathology

Histologic findings in DRESS remain variable, with changes involving both the epidermis and dermis. No pathognomonic feature has been identified; however, according to Sasidharanpillai et al., the presence of varying combinations of epidermal hyperplasia, spongiosis, and parakeratosis, in the background of a lymphocyte-predominant dermal infiltrate with occasional atypia, may favor a diagnosis of DRESS in the appropriate clinical setting.[15] In relation to our case, the findings paralleled those described by Sasidharanpillai et al., particularly the presence of interface change, lymphocyte exocytosis, and a lymphocyte-predominant infiltrate.[15] Although epidermal hyperplasia and parakeratosis were absent, the combined histologic and clinical features were consistent with the diagnosis observed in our patient.

Meanwhile, in the early stages of SJS/TEN, the epidermis shows sparse apoptotic keratinocytes within the suprabasal layers. With disease progression, epidermal detachment and epidermolysis develop, accompanied by subepidermal vesiculation from extensive vacuolar alteration and confluent keratinocyte necrosis. Apoptosis may also involve adnexal structures. The papillary dermis typically demonstrates a moderately dense mononuclear infiltrate, mainly lymphocytes and macrophages, with occasional eosinophils and extravasated erythrocytes.[11] In our patient, the biopsy revealed full-thickness epidermal necrosis with confluent necrotic keratinocytes and prominent vacuolar interface changes, findings that parallel those described in SJS/TEN.

History and Physical Examination

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) typically develops 2–8 weeks after drug exposure and may present with or without cutaneous involvement. Prodromal features include fever, malaise, and pruritus, followed by widespread eruptions that may affect more than 50% BSA, often progressing to erythroderma in a subset of cases. Characteristic findings include symmetrical facial edema, mucosal involvement, and generalized lymphadenopathy.[12]

Systemic manifestations are frequent, occurring in up to 90% of patients, with the liver most commonly affected. Hepatitis with persistent elevation of liver enzymes is the hallmark feature, however, involvement of the kidneys, lungs, heart, and endocrine system are also often present. Renal impairment is usually mild but may progress to interstitial nephritis, while pulmonary manifestations range from cough to pleural effusion. Cardiac complications, including eosinophilic myocarditis, though rare, may be life-threatening. Endocrine sequelae such as thyroiditis can develop months after resolution and warrant long-term monitoring.[12]

Hematologic findings are notable for eosinophilia in the majority of cases, accompanied by leukocytosis or transient cytopenias. Symptoms may persist even after discontinuation of the offending drug, highlighting the protracted and relapsing nature of DRESS and the importance of prolonged surveillance for late-onset organ involvement.[12]

In our patient, lymphadenopathy, eosinophilia, skin involvement >50% body surface area, skin lesions suggesting DRESS, and organ involvement were present yielding a RegiSCAR of 4 corresponding to a possible case of DRESS.

Epidermal necrolysis, encompassing Stevens–Johnson syndrome (SJS), SJS–TEN overlap, and toxic epidermal necrolysis (TEN), is a severe cutaneous adverse reaction (SCAR) classified by the extent of skin detachment: <10% BSA in SJS, 10–30% in overlap, and >30% in TEN. Onset usually occurs within four weeks of drug exposure, often preceded by nonspecific prodromal symptoms. The disease typically begins with erythematous macules that evolve into bullae, epidermal detachment, and mucosal erosions, with a positive Nikolsky sign. Mucous membrane involvement is seen in most patients, commonly affecting ocular and oral sites, sometimes leading to long-term sequelae.[12]

Systemic complications are common and may involve the respiratory tract, gastrointestinal system, and kidneys. Symptoms include fever, malaise, ocular stinging, photophobia, and painful erosions. Laboratory findings

are nonspecific, though hematologic, hepatic, and renal abnormalities may indicate organ involvement. Prognostication relies on validated severity scoring systems, with SCORTEN being the most widely used and consistent predictor of mortality.[12]

In relation to our patient, she noted severe stinging pain and skin fragility, characterized by detachment of the skin upon removal of clothing, febrile episodes, chills, odynophagia, dysphagia and dysgeusia. Upon physical examination erythematous patches with erosions and overlying yellowish crusts developed on the medial upper eyelids, accompanied by mucoid discharge, along with increased crusting of previous lip lesions. These findings are consistent with SJS-TEN.

Treatment and Management

Management of DRESS and SJS/TEN shares key principles, including early withdrawal of the culprit drug, close monitoring for systemic complications which often requires intensive care unit (ICU) management and supportive care such as wound care, fluid and electrolyte management, and nutritional support. Immunomodulatory therapy may be considered in severe cases, though regimens differ between conditions. In DRESS, systemic corticosteroids are most commonly used to control acute symptoms and prevent long-term autoimmune complications, with alternatives such as cyclosporine or N-acetylcysteine in selected cases. For SJS/TEN, corticosteroids may offer benefit if started early, but infection risk remains a concern; cyclosporine and TNF-α inhibitors (etanercept, infliximab) have shown promising outcomes in reducing disease progression and hospitalization, while IVIg has not demonstrated consistent survival benefit.[12]

Clinical Course and Prognosis

While there are no available markers to predict disease outcomes,[7] the clinical course and prognosis of DRESS vary across drugs. Prognosis tends to be better when the offending drug is immediately identified and withdrawn at the acute phase, and adequate treatment has been initiated. However, despite discontinuation of the offending drug, relapses may still occur, as there is a latency period between drug administration and onset of the disease.[6] Laboratory investigations are often performed at a later time when DRESS is already suspected, as the onset of cutaneous lesions has happened much earlier, contributing to longer latency time.[1] While mortality is reported at only 3.8%, it remains to be the most unfavorable complication of DRESS which is secondary to fulminant hepatitis or heart failure, other indicators for poor prognosis include eosinophil count greater than 6000 x 10^3/uL, thrombocytopenia, leukocytosis and coagulopathy.[2] In this context, the present case underscores the likelihood of DRESS secondary to fenofibrate. Previous reports have documented cases of hepatitis and eosinophilia occurring without skin manifestations, and Safrano et al. (2014) noted that fenofibrate may induce DRESS.[14] They emphasized the importance of clinician awareness of this potential adverse effect to allow prompt drug withdrawal at the onset of suggestive symptoms and thereby prevent serious outcomes.

Case Relevance

This case emphasizes that DRESS and TEN are not always distinct conditions but may lie on a clinical continuum. Sequential clinical reassessment, structured use of diagnostic tools (RegiSCAR, SCORTEN), and early recognition of drugs with higher risk profiles, such as Fenofibrate, are critical for timely management. This case illustrates the rare progression of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) to Toxic Epidermal Necrolysis (TEN). Such sequential evolution is uncommon but clinically important, as it highlights the dynamic spectrum of severe cutaneous adverse reactions. The diagnosis was supported by histopathologic findings that documented features of both DRESS and TEN at different stages, making this report particularly significant. Using the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN),[16] Fenofibrate scored 7 (very probable), Leflunomide scored 4 (probable), and Semaglutide scored 2 (possible). Hence, Fenofibrate was identified as the most likely culprit drug. However, the probability of causality from Leflunomide (probable) and Semaglutide (possible) cannot be entirely ruled out, particularly as all three drugs were initiated simultaneously. Notably, the presence of ankylosing spondylitis, an autoimmune disease, may have predisposed the patient to an increased risk of drug eruptions. By capturing this progression, the case highlights the importance of early recognition, vigilant monitoring, and timely intervention in patients with severe drug reactions, ultimately contributing to better understanding and management of these life-threatening conditions.

SUMMARY AND CONCLUSION

This case highlights a rare but fatal instance of probable Fenofibrate-induced DRESS progressing to TEN. Recognition of culprit drugs, such as Fenofibrate, is critical. Early withdrawal, prompt treatment, and structured application of RegiSCAR and SCORTEN can guide prognosis and management. Despite multidisciplinary interventions, mortality remains high once progression to TEN occurs.

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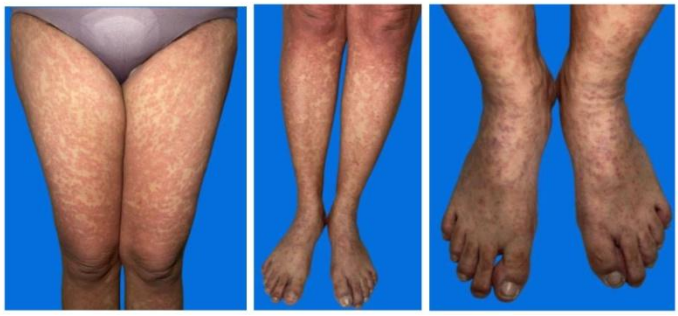
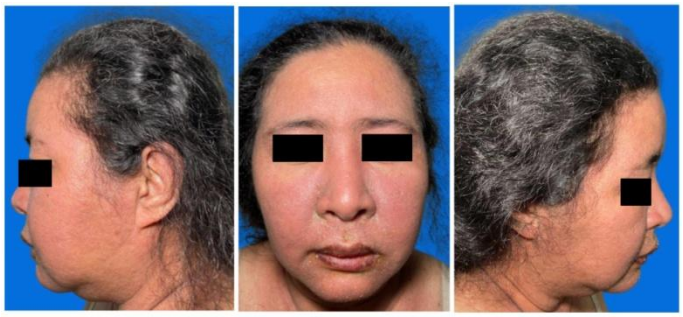
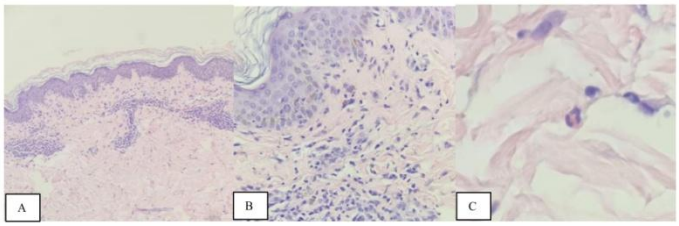
FIGURES



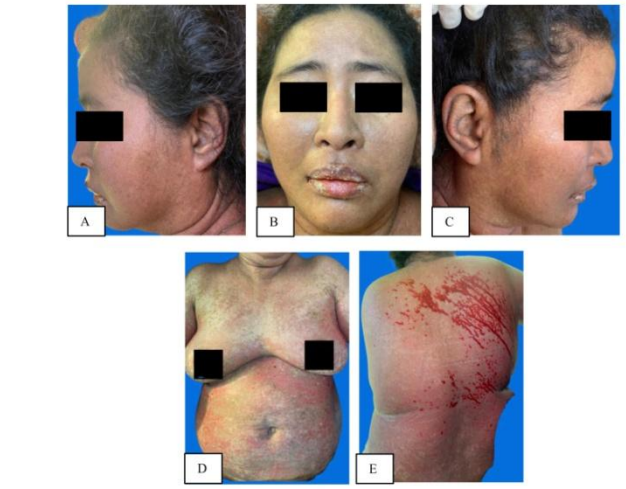
[Figure 1]. Images upon referral. Multiple, well-defined, erythematous, some dusky macules & papules coalescing into patches and plaques. Multiple, well-defined, erythematous, non-blanching macules.

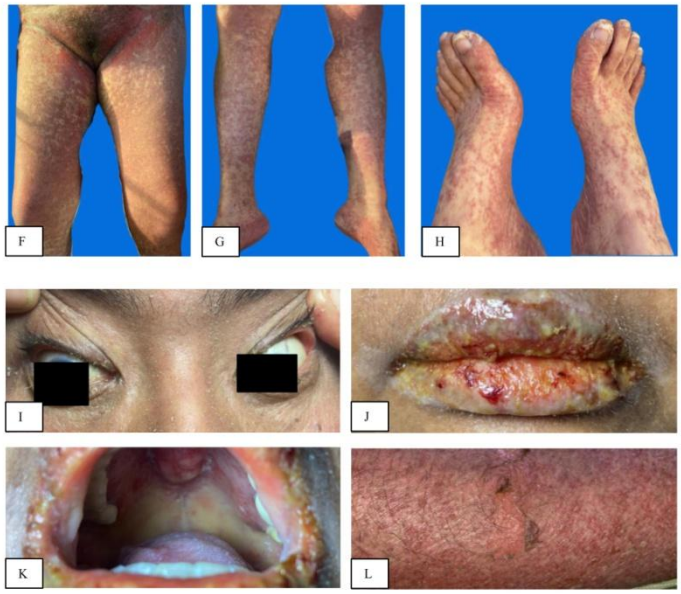


[Figure 2]. Image shows facial edema and cheilitis with crusting and fissuring of the lips.

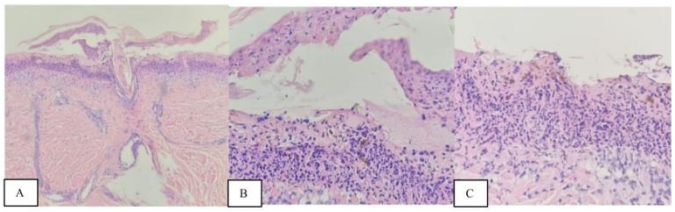


[Figure 3]. Initial skin biopsy (H&E staining). (A) Normal epidermal thickness with basketweave orthokeratosis, (B) focal vacuolar alteration with lymphocytic exocytosis at the dermoepidermal junction, and superficial perivascular lymphocytic infiltrates with scattered (C) eosinophils.





[Figure 4]. Images on fourteenth day of admission. (A-H) Increase in erythema and scaling of the previous lesions on the trunk with noted bleeding points, (I) yellowish crusting of the eyelid, (J) hemorrhagic crust and suppuration of the lips, (K) whitish patch on the palate, and (L) positive Nikolsky sign



[Figure 5]. Repeat skin biopsy (H&E staining). (A) Full-thickness epidermal necrosis with confluent necrotic keratinocytes, (B) linear neutrophilic infiltrates at the basal epidermis, (C)prominent vacuolar interface change, dermal edema, sparse superficial perivascular lymphocytes,

APPENDIX A
Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN)

Criterion	Values	Rules to apply	Range	Patient Score
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	–3 to 3	+2
	Compatible +2	From 29 to 56 days		
	Likely +1	From 1 to 4 days		
	Unlikely –1	>56 Days		
	Excluded –3	Drug started on or after the index day		
		In case of previous reaction to the same drug, only changes for: Suggestive: +3 (1–4 days), Likely: +1 (5–56 days)		
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped <5× elimination half-life[a] before index day	–3 to 0	0 (Fenofibrate, Leflunomide, Semglutide)
	Doubtful –1	Drug stopped >5× elimination half-life[a] but with organ dysfunction or drug interactions[b]		
	Excluded –3	Drug stopped >5× elimination half-life[a] without dysfunction or interactions[b]		
Prechallenge/ rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	–2 to 4	+4 (Fenofibrate)
	Positive specific for disease or drug: 2	SJS/TEN after similar[c] drug or other reaction with same drug		Not done/ unknown (Leflunomide, Semglutide)
	Positive unspecific: 1	Other reaction after similar[c] drug		
	Not done/unknown: 0	No known previous exposure		
	Negative –2	Exposure without reaction		
Dechallenge	Neutral 0	Drug stopped (or unknown)	–2 or 0	0
	Negative –2	Drug continued without harm		
Type of drug (notoriety)	Strongly associated 3	"High-risk" drug per case–control studies[d]	–1 to 3	+ 1 (Fenofibrate)
	Associated 2	Definite but lower risk drug per case–control studies[d]		+2 (Leflunomide)
	Suspected 1	Several reports, ambiguous epidemiology (drug "under surveillance")		
	Unknown 0	All other drugs including newly released ones		0 (Semglutide)
	Not suspected –1	No evidence of association from previous epidemiology study[e] with sufficient exposed controls[c]		
Other cause	Possible –1	Rank all drugs from highest to lowest intermediate score. If ≥1 drug score >3, subtract 1 from others.	–1	0
Final score	—	Total of all criteria	–12 to 10	**7 (Fenofibrate) Very Probable** **4 (Leflunomide) Probable** **2 (Semaglutide) Possible**

Final score –12 to 10
<0, very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable.[16]