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CASE REPORT

Upadacitinib Coadministered with Methylprednisolone for Effective Treatment of SJS/TEN Overlap Syndrome: A Case Report

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Abstract: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) overlap syndrome, characterized by extensive epidermal necrosis, represents a life-threatening severe dermatological disorder.Therapeutic agents and regimens for this condition include high-dose glucocorticoids, intravenous immunoglobulin (IVIG), plasma exchange, immunosuppressants, and TNF-α inhibitors. A study demonstrates that JAK/STAT hyperactivation—characterized by interferon signature enrichment, STAT1 phosphorylation in keratinocytes/macrophages, and subsequent GBP1/WARS1-mediated cytotoxicity—drives epidermal detachment in TEN. JAK inhibitors (including JAK1-selective agents) suppressed this pathway in murine models and achieved rapid resolution in seven TEN patients.Recent clinical studies have demonstrated the therapeutic efficacy of JAK inhibitors in SJS/TEN management. In this context, we present the case of a 54-year-old woman who presented to the hospital with a 6-day history of rapidly worsening erythema, accompanied by a 4-day history of blistering and erosion. The patient received treatment with methylprednisolone (40 mg/day, weight: 49 kg) and upadacitinib (15 mg/day for 2 weeks). Combination therapy achieves rapid disease control by halting the progression of cutaneous necrosis while enabling accelerated glucocorticoid tapering. This case underscores that the combination therapy of upadacitinib and methylprednisolone can offer a promising approach for the SJS/TEN overlap syndrome.

Keywords: SJS/TEN overlap syndrome, upadacitinib, methylprednisolone

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) overlap syndrome is characterized by extensive epidermal necrosis, resulting in the separation of the epidermis from the underlying dermis, affecting 10% to 30% of the body surface area.[1] A hallmark of this disease is rapidly progressive cutaneous necrosis. When a drug or its metabolite functions as an antigen or hapten to activate cytotoxic $CD8^+$ T lymphocytes, these $CD8^+$ T cells and natural killer (NK) cells produce Fas ligand (FasL). FasL engages Fas receptors on target cells, inducing apoptosis via either the Fas-FasL pathway (activating the caspase cascade) or the perforin/granzyme pathway.[2,3] $CD8^+$ T-cells are recruited to the epidermis, where interferon-γ is released, activating the JAK-STAT Pathway. Janus kinases (JAKs) and signal transducer and activator of transcription (STAT) proteins bind to the intracellular domains of type I and II cytokine receptors, which recognize soluble inflammatory mediators such as interleukins and interferons.[4] Upregulation of signaling proteins in multiple JAK-STAT pathways has been demonstrated in both keratinocytes and immune cells in toxic epidermal necrolysis (TEN).[5] Emerging evidence indicates that activation of the JAK/STAT signaling pathway serves as a key driver in the pathogenesis of toxic epidermal necrolysis (TEN).[5] Moreover, it is noteworthy that HHV-6 reactivation

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during the disease course can further exacerbate organ involvement and prolong the clinical course of SJS/TEN.[6] Failure to achieve timely disease control may result in expansion of epidermal detachment areas and potential visceral involvement. Therapeutic protocols have not yet been standardized, and achieving an optimal balance among therapeutic efficacy, safety profile, and cost-effectiveness remains clinically challenging. Upadacitinib, a selective Janus kinase 1 (JAK1) inhibitor currently approved for rheumatoid arthritis and atopic dermatitis, has emerged as a novel therapeutic candidate for refractory dermatological conditions.[7] Upadacitinib has demonstrated efficacy in improving both the clinical and histological severity of TEN in mouse models.[5] In this report, we present the case of a woman diagnosed with SJS/TEN overlap syndrome who was successfully treated with a combination of Upadacitinib and Methylprednisolone.This breakthrough provides a promising therapeutic alternative for future management of SJS/TEN overlap syndrome.

Case Presentation

A 54-year-old woman presented with a 6-day history of rapidly worsening erythema, accompanied by a 4-day history of blistering and erosion. Physical examination revealed extensive erythema, blisters, and erosions distributed throughout the body. Laboratory tests, including assessments of liver and kidney function, hepatitis B and C antibody tests, and a tuberculosis assay, yielded negative results. Skin biopsy analysis demonstrated extensively necrotic epidermal cells, with blisters forming beneath the epidermis and sparse infiltration of lymphocytes and neutrophils in the superficial dermis. Direct immunofluorescence results were also negative. Initially diagnosed with SJS, the diagnosis was later revised to SJS/ TEN overlap syndrome due to the presence of fulminant epidermal detachment exceeding 10% of the total body surface area (TBSA) (15%) and a SCORTEN score of 1 (Figure 1a). Upon admission, the patient received treatment with methylprednisolone (40 mg/day, weight: 49 kg) and upadacitinib (15 mg/day for 2 weeks). Daily dorsal lesion changes throughout the course of treatment were documented (Figure 1b–o).This regimen resulted in the cessation of disease progression, with erythema regressing within three days after treatment initiation and a 35% reepithelialization rate of the affected skin areas by day 7 (Figure 1h). By day 14 and 22, 100% reepithelialization rate of the isolated skin area was noted (Figure 1o and p). The patient's perioral skin became noticeably dry and crusted on day 2 and day 4, and was completely healed by day 6 (Figure 2). Methylprednisolone was gradually tapered at a rate of 10 mg per week, with no adverse effects reported during therapy and follow-up.

Discussion

SJS/TEN overlap syndrome carries a mortality rate exceeding 30% without rapid intervention.[1] This urgency necessitates both early diagnosis (eg, blister granulysin quantification[8]) and effective therapeutics. Critically, current frontline treatments remain inadequate: High-dose glucocorticoids paradoxically increase mortality risk,[9] while TNF-α inhibitors like etanercept require administration within a narrow 7-day window to reduce mortality from 60% to 10.6%.[10] Even advanced combination regimens report mean re-epithelialization times of 11.8 days[11]—highlighting an unmet need for mechanistically targeted alternatives.

Given these limitations, therapies directly targeting the core inflammatory cascade driving SJS/TEN pathogenesis are urgently needed. In this context, recent spatial proteomics by Nordmann et al provides a mechanistic foundation for JAK inhibitor therapy.[3] Their work demonstrates that JAK/STAT hyperactivation—characterized by interferon signature enrichment, STAT1 phosphorylation in keratinocytes/macrophages, and subsequent GBP1/WARS1-mediated cytotoxicity—drives epidermal detachment in TEN. Crucially, JAK inhibitors (including JAK1-selective agents) suppressed this pathway in murine models and achieved rapid resolution in seven TEN patients.[5]

In this first-reported application of upadacitinib for SJS/TEN overlap syndrome, we selected the Upadacitinib as the JAK inhibitor in this case for three primary reasons: (1) Pathway precision: Direct inhibition of the core JAK/STAT-IFNγ axis vs upstream cytokine blockade; (2) Dosing efficiency: 15 mg/day efficacy without initial load-doubling required by other JAKi; (3)Steroid-sparing capacity: Enabled 50% methylprednisolone reduction within 72 hours. This approach yielded clinical stabilization within 48 hours and complete re-epithelialization by Day 16 in a patient with 35% BSA involvement.

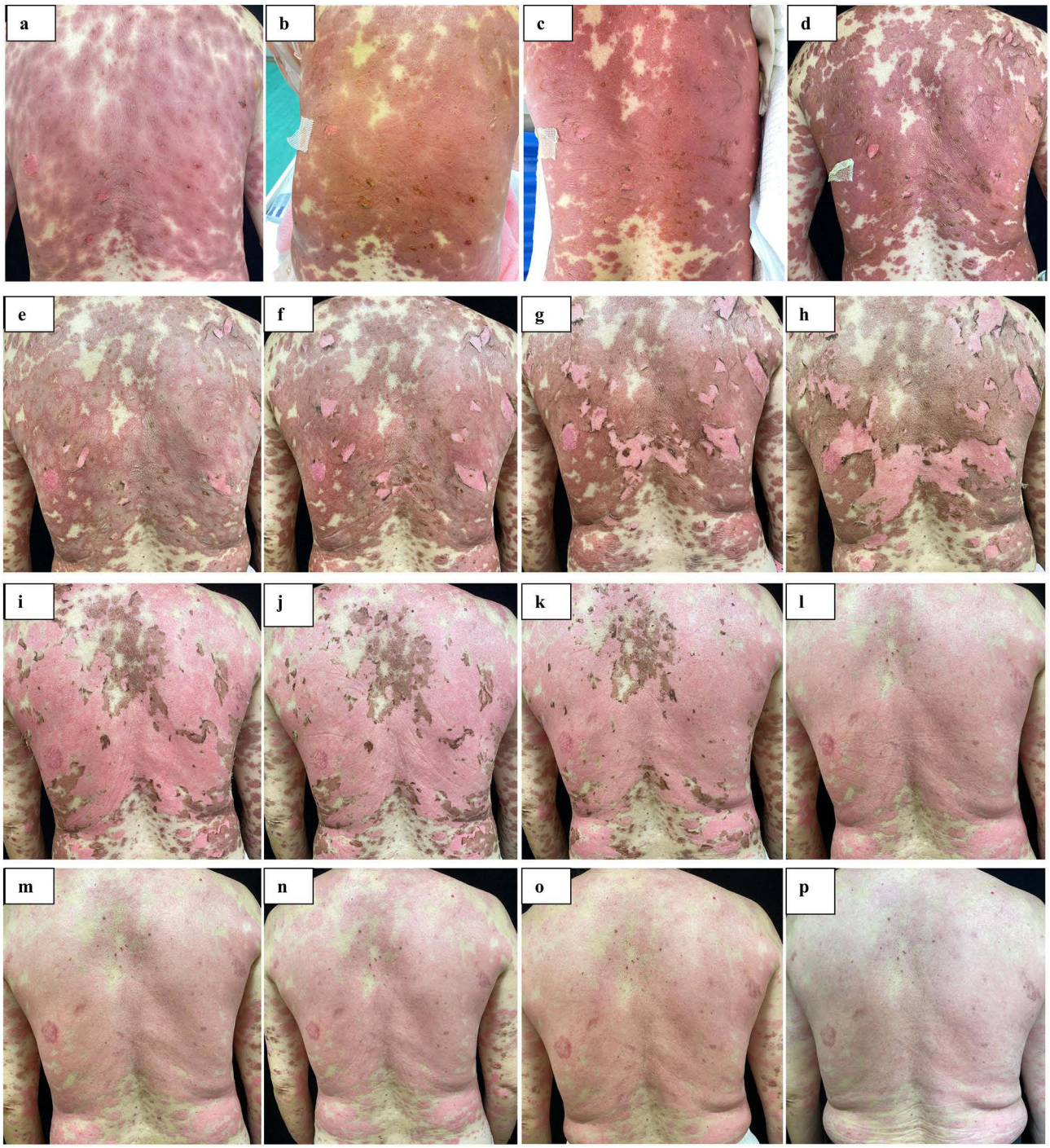

Figure 1 Clinical Images of the Back before and After treatment. (**a**) Pretreatment clinical image; (**b–o**) Posttreatment clinical image from day 1 to 14; (**p**) Posttreatment clinical image at day 22.

While evidence for JAK inhibitors in SJS/TEN remains investigational,[7] our case aligns with preclinical and emerging clinical data,[5] supporting their role as mechanistically targeted alternatives to cytokine blockers. Prospective multicenter trials should establish optimal dosing and compare efficacy against biologics in high-risk subgroups.

An important consideration arising from this case is whether JAK inhibitor monotherapy could achieve comparable efficacy without concomitant steroids. Preclinical evidence suggests this may be feasible: Nordmann et al demonstrated significant disease amelioration with JAK inhibitor monotherapy in murine TEN models.[3] However, given the life-

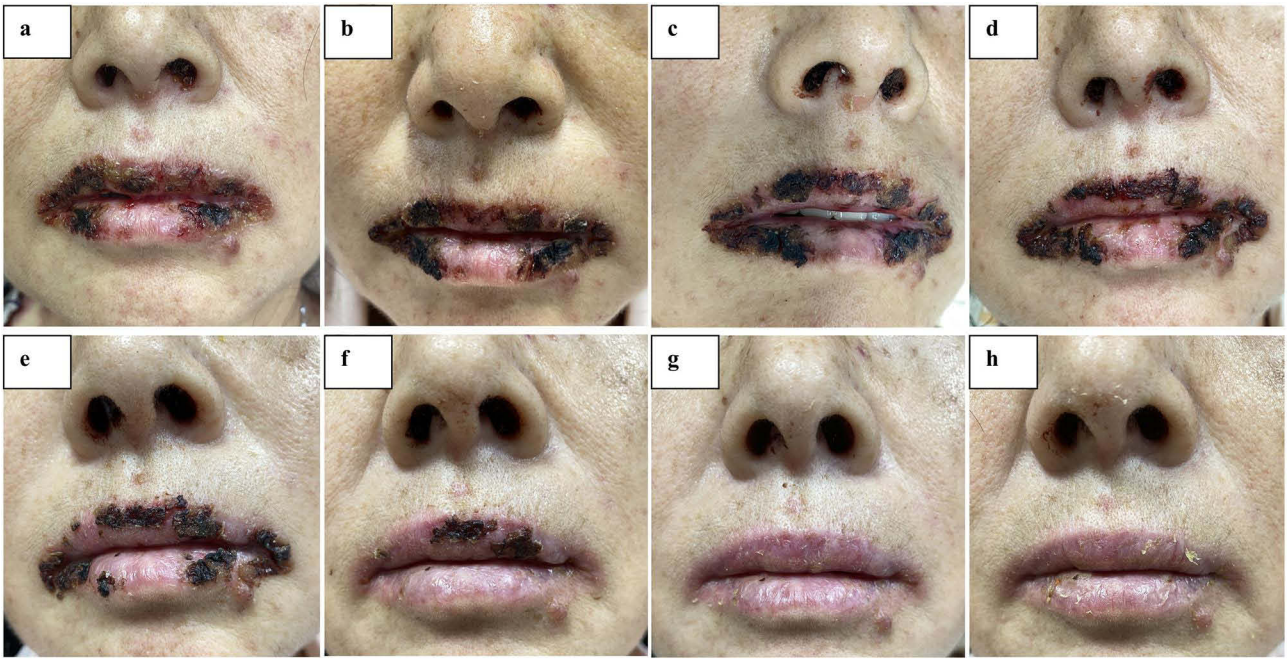

Figure 2 Clinical Images of the lip Before and After treatment. (**a**) Pretreatment clinical image; (**b–h**) Posttreatment clinical image from day 1 to 7.

threatening nature of human SJS/TEN and current limited clinical experience, we maintained combination therapy as a precautionary measure.This critical question warrants dedicated investigation through controlled trials. Our future research will systematically evaluate the efficacy and safety of JAK inhibitor monotherapy in SJS/TEN, with a focus on upadacitinib as a potential standalone intervention for early-stage disease.

Conclusion

In conclusion, the management of SJS/TEN overlap syndrome remains a clinical challenge. Our case report demonstrates the potential of upadacitinib as a promising therapeutic agent, which may significantly reduce corticosteroid dosage requirements. However, further large-scale clinical studies are warranted to validate its therapeutic efficacy and long-term safety profile in this severe dermatological condition.

Abbreviations

SJS, Stevens-Johnson syndrome; TEN,toxic epidermal necrolysis.

Ethics Statement

The patient provided written informed consent for publication of this report and accompanying images. The Ethics Committee of Jiangxi Provincial Dermatology Hospital, has approved the publication of the case details.

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Disclosure

The authors report no conflicts of interest in this work.

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