

Allopurinol-Induced Toxic Epidermal Necrolysis Following A Sub-Minimal Starting Dose: A Multidisciplinary Management Challenge

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ABSTRACT

Toxic Epidermal Necrolysis (TEN) is a rare, severe mucocutaneous drug reaction within a single clinical spectrum, distinguished by epidermal detachment involving >30% of body surface area (BSA). Allopurinol is among the most common causative agents, particularly in patients newly started on therapy, and carries a well-established pharmacogenomic association with the HLA-B*58:01 allele. We present the case of a 55-year-old woman with newly diagnosed hyperuricemia who developed generalized pruritus within hours of taking half of a 300-mg allopurinol tablet, followed by burning in the bilateral axillary and inguinal regions and erythema of the trunk and abdomen. Within hours, she developed flaccid bullae with a positive Nikolsky sign, together with periorbital, conjunctival, oral, and vulvovaginal mucosal involvement. She was admitted to the intensive care unit with a diagnosis of Stevens-Johnson syndrome, an initial epidermal detachment under 10% of body surface area, and a SCORTEN of 1 (predicted mortality 3.2%). Gynecology was consulted for vulvovaginal ulceration and atrophic mucosa. Cutaneous detachment progressed to involve approximately 40-50% of BSA, requiring three staged surgical washouts and debridements with application of a porcine-derived extracellular matrix wound dressing to promote re-epithelialization. The hospital course was further complicated by transient vasopressor-requiring hypotension, chronic hypo-osmolar hyponatremia, probable relative adrenal insufficiency following corticosteroid tapering, opioid-associated ileus, and recurrent hypoglycemia, all managed supportively without evidence of superimposed infection. After 15 days in the intensive care unit, the patient was transferred to the internal medicine ward with favorable re-epithelialization of cutaneous lesions and resolution of cervicovaginitis. This case illustrates the fast development and multisystem nature of allopurinol-induced SJS/TEN overlap and the value of early, protocolized multidisciplinary management.

KEYWORDS: Stevens-Johnson syndrome, toxic epidermal necrolysis, allopurinol, SCORTEN, vulvovaginal involvement, extracellular matrix dressing.

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I. INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent a single spectrum of rare, severe, immune-mediated mucocutaneous reactions, most commonly triggered by medications, and classified by the percentage of body surface area (BSA) with epidermal detachment: SJS

below 10%, SJS/TEN overlap between 10% and 30%, and TEN above 30%¹.

Allopurinol is one of the most frequently implicated agents worldwide, particularly during the first weeks of therapy, constituting a substantial proportion of reported SJS/TEN cases assigned to a single drug².

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Its association with the HLA-B*58:01 allele is one of the best-characterized pharmacogenomic risk factors for a severe cutaneous adverse reaction, with especially high relevance in populations of Han Chinese, Thai, and other Asian ancestries, though cases occur across all ethnicities³.

Prognosis is most commonly estimated using the SCORTEN scale, a validated severity-of-illness score incorporating age, malignancy, heart rate, initial BSA involvement, serum urea, glucose, and bicarbonate, although its accuracy in contemporary intensive care settings has been questioned⁴.

Management of SJS/TEN requires prompt withdrawal of the causative agent and transfer to a burn unit or intensive care setting for supportive care; systemic immunomodulatory agents such as cyclosporine have been increasingly used, with observational evidence suggesting a possible mortality benefit, though high-quality randomized data remain limited⁵.

Mucosal involvement, including ocular, oral, and genital surfaces, is a major determinant of long-term morbidity, and dedicated protocols exist to reduce sequelae such as vaginal adhesions, vulvar scarring, and ocular surface disease⁶.

We report a case of allopurinol-induced SJS/TEN overlap with extensive cutaneous, ocular, oral, and vulvovaginal involvement, managed with a multidisciplinary approach including staged surgical debridement and extracellular matrix wound dressings, to illustrate the diagnostic and management complexity of this life-threatening reaction.

II. CASE REPORT

A. History and Presenting Illness

A 55-year-old woman with newly diagnosed hyperuricemia, started on allopurinol approximately one month prior to presentation, took half of a 300-mg tablet (150 mg) in the morning. Within hours, she developed generalized pruritus, followed by a burning sensation in the bilateral axillary and inguinal regions and erythema of the chest and abdomen. She presented to the emergency department the same day, where she was triaged as low acuity, with vital signs notable only for mild hypotension (blood pressure 88/58 mmHg). She was initially diagnosed with a hypersensitivity reaction and admitted for observation, with diphenhydramine and a systemic corticosteroid started. Within approximately eight hours, she developed flaccid bullae with serous fluid over the trunk and abdomen with a positive Nikolsky sign, prompting concern for a severe cutaneous adverse reaction, including possible toxic epidermal necrolysis or a presentation with overlapping features of drug reaction with eosinophilia and systemic symptoms (DRESS), a distinction that can be clinically difficult early in the course of either condition⁷.

B. Clinical Findings

Over the following hours, the patient developed periorbital and conjunctival erythema with ocular burning, oral discomfort without frank mucosal erosions, and painful vulvar and vaginal erythema, edema, and vesicle formation with epidermal detachment. Cutaneous findings progressed to involve the face, neck, anterior and posterior trunk, left axilla and shoulder (Figure 1), right axilla, shoulder and chest (Figure 2), anterior aspect of the left elbow (Figure 3), abdomen, and inguinal region, with a violaceous, dusky erythema and additional flaccid bullae. Epidermal detachment was initially estimated at under 10% of total BSA. She was admitted to the intensive care unit with a diagnosis of Stevens-Johnson syndrome and a SCORTEN of 1, corresponding to a predicted mortality of 3.2%, showing her age over 40 years as the only positive criterion at that time. A central venous catheter was placed via the right subclavian vein without complication.



Figure 1: Epidermal detachment in the left axilla and shoulder



Figure 2: Epidermal detachment in the right axilla, shoulder and chest.



Figure 3: Epidermal detachment in anterior aspect of the left elbow

C. Diagnostic Evaluation

Initial laboratory studies showed leukocytosis with marked neutrophilia (leukocytes 18,480/ μ L, 92.4% neutrophils), mild azotemia (blood urea nitrogen 29 mg/dL, creatinine 1.02 mg/dL), and preserved hepatic and coagulation parameters. Arterial blood gas analysis showed a mild respiratory alkalosis with adequate oxygenation on supplemental oxygen. Gynecologic evaluation of the vulvovaginal lesions revealed introitus ulceration with atrophic mucosa; the differential at that time included TEN-related mucosal involvement, atrophic vaginitis, and superimposed infection, though no infectious organism was ultimately isolated. Serial complete blood counts and inflammatory markers were followed throughout the admission to monitor for secondary infection, with no evidence of systemic inflammatory response syndrome or a documented infectious focus at any point.

Cutaneous involvement remained evolving over the following two weeks, ultimately obtaining approximately 40-50% of BSA (18% anterior torso, 18% posterior torso, 9% arms, 4% face and neck, and 1% genital region), with partial-thickness dermal loss, areas of granulation tissue, and progressive re-epithelialization at the wound margins.

A skin biopsy was performed, which reported interphase dermatitis with a perivascular pattern.

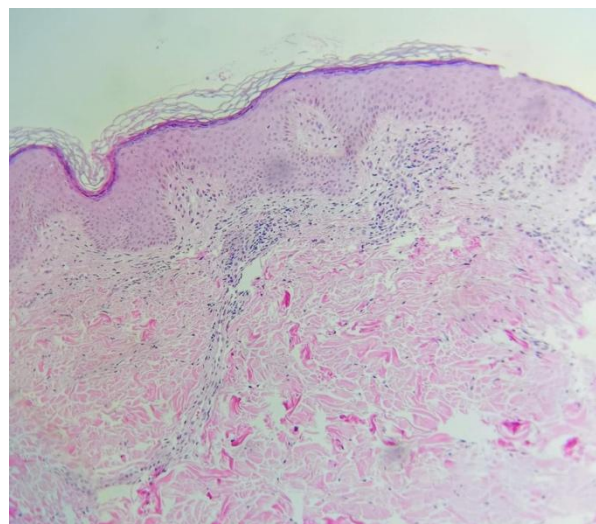


Figure 4: Skin biopsy with slight basal vacuolization of the epidermis, slight focal dyskeratosis, associated with a superficial lymphocytic infiltrate, from scarce to mild.

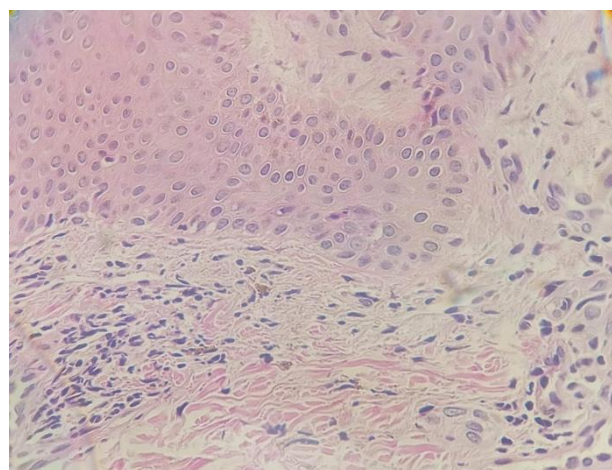


Figure 5: Skin biopsy with melanophages scattered in the papillary dermis as well as the presence of perivascular infiltrate with edematous endothelium.

D. Diagnostic Issues

The principal diagnostic challenge in this case was the quick development of a reaction that initially appeared to be a limited hypersensitivity phenomenon into a life-threatening mucocutaneous emergency within less than 24 hours, necessitating repeated review of the percentage of BSA involved and, consequently, of the patient's prognostic category and SCORTEN-based risk stratification as the disease progressed. A second challenge was distinguishing the vulvovaginal exudate from an active infectious process; the initial appearance was concerning for superimposed candidal or bacterial infection, but following interdisciplinary reassessment, the secretions were attributed to an inflammatory, exudative process compounded by the irritant effect of topical antimicrobial and antifungal agents, prompting de-escalation of vaginal therapy rather than escalation. A third challenge was recognizing iatrogenic complications that imitated or compounded the underlying

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disease, including probable relative adrenal insufficiency following corticosteroid tapering (appearing as recurrent hypoglycemia, hyponatremia, and a declining blood pressure trend) and opioid-associated ileus, both of which required a strong index of suspicion to distinguish from disease-related deterioration or sepsis.

E. Treatment

The causative agent, allopurinol, was discontinued immediately upon suspicion of a severe cutaneous adverse reaction. Supportive management in the intensive care unit included parenteral fluid resuscitation, gastric mucosal protection, thromboprophylaxis, and multimodal analgesia with a continuous intravenous lidocaine infusion, buprenorphine transitioning to tramadol, pregabalin, paracetamol, and clonixinate of lysine, given severe neuropathic and nociceptive pain poorly controlled by initial regimens. Wound care was initially managed with topical silver sulfadiazine and miconazole.

As cutaneous involvement progressed, plastic and general surgery performed three staged surgical procedures under general anesthesia or sedation, consisting of mechanical washout with saline and amikacin, debridement of devitalized tissue, and application of a porcine-derived extracellular matrix wound dressing (Oasis) to deeper dermal wounds, with petrolatum gauze over more superficial lesions, covering the neck, trunk, abdomen, axillae, back, buttocks, popliteal fossae, and genital region; biosynthetic and extracellular matrix dressings of this kind have been reported to allow delayed, staged surgical management of extensive TEN wounds when donor skin for grafting is unavailable⁸.

Gynecology managed the vulvovaginal involvement with combined ketanserin-metronidazole-miconazole vaginal ovules for ten nights, followed by topical estriol cream for vaginal atrophy; vaginal ovules were later discontinued given their irritant potential once active infection was considered unlikely, and conservative local mucosal care was continued. A transient episode of hypotension in the early ICU course required brief low-dose norepinephrine, which was successfully weaned. Vitamin C supplementation was added to support collagen synthesis and cross-linking given ongoing micronutrient losses through wound exudate, and dietary management was adjusted with a fractionated, low-glycemic-index, high-fiber diet to prevent hypoglycemic episodes related to nutritional and endocrine derangements.

F. Follow-Up and Outcome

The patient's cutaneous lesions progressively re-epithelialized over the following two weeks (Figure 6) and the vulvovaginal cervicovaginitis resolved on serial gynecologic reassessment. Hemodynamic stability was achieved without further vasopressor requirement, hyponatremia and hypoglycemic episodes trended toward resolution with supportive management, and opioid-associated constipation improved with prokinetics and

laxatives, allowing progressive mobilization. No systemic infection was documented during the 15-day ICU stay. The patient was transferred to the internal medicine ward in stable condition, tolerating an oral diet, ambulating with assistance, and with pain controlled on oral agents, for continued wound care and monitoring of mucosal healing.

III.DISCUSSION



Figure 6: Re-epithelialization of the skin lesions in the dorsal region two weeks after the hospital discharge.



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This case demonstrates the fast, multisystem evolution characteristic of SJS/TEN and the diagnostic difficulty of accurately staging disease severity when cutaneous and mucosal involvement continues to progress after the initial evaluation. Although the patient's admission SCORTEN of 1 predicted a relatively low mortality risk of 3.2%, her BSA involvement ultimately evolved from an SJS-range presentation to an overlap and near-TEN-range extent of detachment, underscoring that SCORTEN calculated at a single early time point may underestimate the eventual severity and resource requirements of a case, particularly when the reaction is still evolving at the time of initial risk stratification⁶.

Allopurinol remains one of the most frequently implicated drugs in SJS/TEN, and this case illustrates the classically described pattern of reaction onset within the first weeks of therapy in a patient newly started on the medication for hyperuricemia. While HLA-B*58:01 genotyping is not universally available or performed prior to allopurinol initiation outside of specific high-risk populations, this case reinforces the importance of counseling patients on early warning symptoms, such as pruritus, mucosal discomfort, or rash, when starting the drug, so that it can be withdrawn promptly at the first sign of a hypersensitivity reaction [III]. In this patient, HLA-B*58:01 genotyping was not performed because molecular biology testing is not available at our institution; this test should be pursued in hospitals with access to a molecular biology laboratory, particularly before starting allopurinol in patients from high-risk ethnic groups³.

Mucosal involvement, and vulvovaginal involvement in particular, is a frequently underrecognized but clinically important aspect of SJS/TEN management, since inadequate early attention can result in long-term sequelae including vaginal adhesions, stenosis, and chronic dyspareunia⁶. In this patient, early and repeated gynaecologic evaluation allowed the treating team to correctly reinterpret an exudate that initially appeared infectious as an inflammatory and irritant process, avoiding unnecessary escalation of antimicrobial therapy while still providing appropriate local mucosal care and estrogen-based support for the atrophic vaginal mucosa.

Similarly, early ophthalmologic and dermatologic co-management, as recommended in contemporary guidance, is essential to reduce the possibility of chronic ocular surface disease, a leading cause of long-term morbidity after SJS/TEN⁹.

The surgical approach in this case, using serial mechanical debridement with a porcine-derived extracellular matrix wound dressing rather than autografting, reflects an increasingly used strategy for the extensive partial-thickness cutaneous wounds of TEN, with the aim to provide a scaffold for re-epithelialization while limiting donor-site morbidity, which is particularly relevant in a patient without unaffected donor skin available for grafting⁸.

This case also accentuates the importance of anticipating iatrogenic complications inherent to chronic critical illness and its treatment. The clinical picture of recurrent hypoglycemia, hyponatremia, and a declining blood pressure trend following corticosteroid tapering was suggestive of critical illness-related corticosteroid insufficiency, a well-described complication of glucocorticoid withdrawal in critically ill patients that requires immediate recognition to avoid it being mistaken for disease-related deterioration or occult sepsis¹⁰.

Likewise, the opioid-associated ileus observed during this admission shows a well-documented consequence of the multimodal opioid analgesia required for adequate pain control in extensive mucocutaneous disease, and highlights the benefit of proactive bowel regimens and, when needed, opioid-receptor antagonists to prevent and treat opioid-induced bowel dysfunction in critically ill patients¹¹.

IV. CONCLUSIONS

Allopurinol-induced Stevens-Johnson syndrome/toxic epidermal necrolysis overlap can evolve rapidly from a seemingly limited hypersensitivity reaction into a life-threatening, multisystem emergency, and accurate prognostication requires ongoing reassessment of body surface area involvement rather than reliance on a single early SCORTEN calculation. Favourable outcomes depend on early multidisciplinary management spanning critical care, plastic and general surgery, gynecology, ophthalmology, and pain medicine, with particular attention to mucosal surfaces, wound care strategies such as extracellular matrix dressings for extensive partial-thickness loss, and vigilance for iatrogenic complications arising during prolonged supportive treatment. Clinicians prescribing allopurinol should maintain a low threshold for early discontinuation at the first sign of a hypersensitivity reaction, particularly during the initial weeks of therapy.

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