International Journal of Pharmaceutical research and Applications
Volume 10, Issue 3, May-June 2025, pp:1003-1007 www.ijprajournal.com ISSN: 2456-4494

"Allopurinol-Induced Stevens-Johnson Syndrome: A Case Report"

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Date of Submission: 20-05-2025 Date of Acceptance: 01-06-2025

ABSTRACT: Allopurinol is a commonly prescribed xanthine oxidase inhibitor for the treatment of gout and hyperuricemia. While generally well tolerated, it is a major source of severe cutaneous adverse effects, including Stevens-Johnson Syndrome (SJS). SJS is an uncommon, potentially fatal mucocutaneous reaction that is frequently associated with high-dose therapy, renal impairment, or genetic predispositions like the HLA-B*58:01 variant.

We present the case of a 62-year-old male with a history of gout and hypertension who experienced SJS one week after starting low-dose allopurinol (100 mg/day). The patient came with a high temperature, severe bullous eruptions, and erythematous rashes covering around 8% of the total body surface area. Leukocytosis and high C-reactive protein levels were found in the laboratory, but renal and hepatic function were normal. The patient was immediately taken off allopurinol and treated with systemic corticosteroids, intravenous fluids, antibiotics, and supportive care. Within 10 days, the patient had complete re-epithelialization and was discharged in stable condition.

This example demonstrates that allopurinol-induced SJS can develop at low dosages and without identified risk factors. It emphasizes the need of early detection, immediate removal of the offending agent, and aggressive supportive management. The instance also emphasizes the importance of clinical monitoring and pharmacogenetic screening, especially in susceptible populations.

I. INTRODUCTION:

Allopurinol, a xanthine oxidase inhibitor, is extensively used to treat gout and chronic hyperuricemia. Its therapeutic efficacy is based on preventing the conversion of hypoxanthine to xanthine and uric acid, which reduces serum urate levels. Despite being a well-known urate-lowering medication, allopurinol is one of the most commonly linked pharmaceuticals to severe cutaneous adverse responses (SCARs), specifically Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) [1,2].

SJS is an immune-mediated mucocutaneous syndrome that causes epidermal necrosis, detachment of less than 10% of the total body surface area (TBSA), mucosal erosions, and systemic symptoms such as fever and malaise [3]. It is frequently regarded part of a spectrum that includes TEN, which contains more than 30% TBSA. Both disorders are associated with substantial morbidity and death, with SJS mortality ranging from 5-10% and TEN up to 30% [4].

The etiology of SJS is complex, with medicines accounting for more than 80% of cases [5]. Allopurinol has continuously been recognized as the most commonly related drug with SJS/TEN in different locations, including Asia and Europe. The EuroSCAR project, a multinational case-control study, found that 17.4% of community-acquired SJS/TEN cases were connected to allopurinol, with an adjusted risk ratio of 18 (95% CI: 11-32) when compared to matched controls [2]. Patients receiving dosages of ≥200 mg/day, having renal insufficiency, or having the HLA-B*58:01 allele are at a significantly higher risk [6].

Allopurinol hypersensitivity is largely determined by genetic predisposition. The HLA-B58:01 allele is substantially related with allopurinol-induced SJS/TEN, especially in the Han Chinese, Korean, and Thai populations. Meta-analyses have revealed odds ratios greater than 75 for HLA-B58:01 carriers [7]. As a result, pre-treatment pharmacogenetic testing is now suggested for high-risk ethnic groups [8].

The primary method for diagnosing SJS is clinical, with targetoid lesions, blistering, mucosal involvement, and a positive Nikolsky sign. Skin biopsy is a confirmatory test that usually reveals full-thickness epidermal necrosis, subepidermal bullae, and a scant lymphocytic infiltration. Laboratory results may show leukocytosis, increased CRP, and electrolyte imbalances. The SCORTEN grading system is often used to determine severity and prognosis, and it takes into account criteria such as

International Journal of Pharmaceutical research and Applications
Volume 10, Issue 3, May-June 2025, pp:1003-1007 www.ijprajournal.com ISSN: 2456-4494

age, serum creatinine, and the amount of skin detachment [9].

Treatment is dependent on the immediate withdrawal of the offending agent, which is the most critical step in preventing illness progression. Fluid resuscitation, temperature control, pain management, nutritional support, and infection prevention are all examples of supportive care in intensive care or burn units [10]. Pharmacologic therapies, including systemic corticosteroids, cyclosporine, TNF-α inhibitors (e.g., etanercept), and IVIG, have been used, but their effectiveness is still contested. Among these, early cyclosporine treatment has showed promise in lowering mortality and hastening re-epithelialization [11,12].

This report describes a rare case of allopurinol-induced SJS at a low dose (100 mg/day) in a patient with no genetic or renal predisposition, emphasizing the importance of close monitoring during the early stages of treatment and reconsidering allopurinol use in patients who do not have clear indications.

II. CASE SUMMARY:

A 62-year-old male weighing 78 kg and with a history of gout and hypertension went to the outpatient department (OPD) with complaints of high fever, painful blisters, and erythematous rashes involving the chest and upper limbs. The symptoms began seven days after starting allopurinol 100 mg once daily for gout. Amlodipine 10 mg OD was also prescribed for hypertension, as was prescribed colchicine 0.6 mg OD for gout.

The patient was diagnosed with gout a few days before and started taking oral allopurinol (Zyloric®, 100 mg). There was no known drug allergies recorded. On the seventh day of medication, the patient developed generalized erythematous macules and bullous lesions on the chest and upper extremities, along with malaise and fever (T: 101°F). Mucosal involvement was restricted to mild conjunctival erythema. Physical examination indicated targetoid lesions with early vesiculation that covered about 8% of the total body surface area (TBSA). The patient's vital signs were stable, BP: 134/86 mmHg and pulse: 98 bpm. There was no evidence of renal impairment or systemic instability.

Laboratory tests revealed leukocytosis (WBC count: 14,800/µL) and increased CRP (68 mg/L) levels. Renal and liver functions are within normal range; HIV, HSV, and Mycoplasma: Negative. On the OPD visit day allopurinol was promptly withdrawn and the patient was admitted for inpatient care. Management included: IV fluids and supportive treatment, Systemic corticosteroids: Methylprednisolone 1 mg/kg/day, Broad-spectrum antibiotics: Ceftriaxone 1g IV twice daily (empiric). Topical emollients for mucosal care (Aquaphor).

By day six, the patient's lesions had stabilized and begun to re-epithelialize. During the hospitalization, no fresh skin detachments were observed. On day 10 after admission, the patient was discharged with full recovery and counseling to permanently avoid allopurinol. According to causality assessment scale (Naranjo scale) the score is 7 (probable). This case demonstrates a rare but severe cutaneous adverse drug reaction to allopurinol at a low dose in a patient with no predisposing genetic (HLA-B*58:01) or renal risk factors, emphasizing the importance of heightened vigilance during the early initiation phase of therapy, even in presumed low-risk patients.

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given? *	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
			Total Score:	7

*Question 6 refers to a typical clinical trials situation and is included here for completeness.

Total Score	Interpretation of Scores
≥ 9	Definite. The reaction (1) followed a reasonable temporal sequence after drug exposure had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, (3) was confirmed by improvement on withdrawing the drug and (4) reappeared on reexposure.
5 - 8	Probable. The reaction (1) followed a reasonable temporal sequence after a drug exposure, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
1 - 4	Possible. The reaction (1) followed a temporal sequence after a drug exposure, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
≤ 0	Doubtful. The reaction was likely related to factors other than a drug.

The Naranjo scale is a tool to help clarify how to evaluate a potential causal association. It is not intended to solve all the complex problems of identification and classification of ADRs.

Figure1: Naranjo Scale

III. DISCUSSION:

Stevens-Johnson syndrome (SJS) is an uncommon but severe cutaneous adverse drug reaction (SCAR) that causes significant epidermal detachment, mucosal involvement, and systemic symptoms such fever and malaise. SJS and its more severe variation, toxic epidermal necrolysis (TEN), are linked to significant morbidity and mortality, with fatality rates of up to 10% in SJS and more than 30% in TEN [13].

Allopurinol, a xanthine oxidase inhibitor commonly used to treat gout and hyperuricemia over time, is one of the most common causes of SJS around the world. A major multinational case-control

International Journal of Pharmaceutical research and Applications
Volume 10, Issue 3, May-June 2025, pp:1003-1007 www.ijprajournal.com ISSN: 2456-4494

study (EuroSCAR) revealed allopurinol as the most common medicine related with SJS/TEN across Europe and Israel, particularly during the first two months of treatment [14]. High beginning doses (>200 mg/day), renal impairment, and the presence of the HLA-B*58:01 allele, which is particularly common in Han Chinese, Thai, and Korean populations, are all risk factors for allopurinol-induced SJS [15,16].

Allopurinol-induced SJS is classified as a type IVc hypersensitivity reaction, mostly mediated by cytotoxic CD8+ T cells. The drug or its metabolite, oxypurinol, can accumulate in individuals, particularly those with renal failure, and behave as a hapten, binding to endogenous proteins. These hapten-protein complexes are displayed on MHC class I molecules, which activates drug-specific cytotoxic T lymphocytes [17]. Consequently, these T cells release pro-apoptotic mediators. Granulysin has been identified as a major cytotoxic molecule that causes extensive keratinocyte death and epidermal detachment in SJS and TEN [18]. Perforin and Granzyme B induce keratinocyte death via intracellular damage. TNF-α and IFN-γ promote local inflammation and increase keratinocyte susceptibility. The Fas-FasL connection initiates extrinsic apoptotic signalling, which contributes to epidermal loss [19].

Pharmacogenetic connections have been well documented, particularly with HLA-B*58:01. According to Kaniwa et al., 40% of Japanese patients with allopurinol-related SJS/TEN carry HLA-B58:01 [20]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) suggests *routine screening for HLA-B58:01 before commencing allopurinol in high-risk ethnic populations*, which has already resulted in a significant reduction in SCAR incidence in Taiwan [21]. Interestingly, the patient in this case got SJS while taking low-dose allopurinol (100 mg/day) and had no recognized risk factors such as renal impairment or HLA-B*58:01 status. This emphasizes the unexpected nature of idiosyncratic medication reactions and the importance of universal therapeutic vigilance, independent of patient risk profile.

The initial and most important step in SJS therapy is to discontinue the offending substance immediately, since this dramatically slows progression and improves prognosis [22]. Once SJS is suspected or diagnosed, the patient should be treated in a burn unit or intensive care unit using a multidisciplinary approach. Supportive management remains the cornerstone of therapy. Fluid and electrolyte replacement, Nutritional assistance, Wound treatment with non-adherent dressings, Temperature management, Pain medication and psychological support Secondary infections, which are a leading cause of death in SJS, must be prevented and managed effectively [23].

The use of systemic corticosteroids, such as methylprednisolone, is still contested, but it is widely used, particularly when started early. Several observational studies indicate that short-term steroid medication may minimize illness progression and hospital stay while not significantly raising infection risk [24]. Recent studies suggest the use of cyclosporine (3-5 mg/kg/day) because of its T-cell inhibitory activity, which prevents granulysin release and lowers keratinocyte death. A meta-analysis found that cyclosporine treatment resulted in a substantial reduction in mortality and faster re-epithelialization than supportive care alone [25].

Intravenous immunoglobulin (IVIG) has been utilized to inhibit Fas-induced apoptosis. However, randomized studies and meta-analyses have found uneven mortality benefits, restricting its use as a first-line therapy [26]. Etanercept, a TNF-α blocker, has showed promise in lowering skin healing time and inflammation in recent trials, making it a feasible alternative in selected individuals [27].

Empirical broad-spectrum antibiotics (such as ceftriaxone) should only be used when an infection is proven or highly suspected. Ophthalmologic treatment is critical, considering the high incidence of ocular involvement in SJS, which can result in permanent vision damage if not treated promptly [28]. To recover from allopurinol-induced SJS, patients should: Avoid allopurinol and related agents, Document adverse reactions in medical records, Counsel on early detection of recurrence, identify medical alerts, Consider HLA screening for family members (if applicable and affordable).

IV. CONCLUSION:

Allopurinol remains a cornerstone in the long-term therapy of gout and hyperuricemia, although its link with potentially fatal hypersensitivity responses like Stevens-Johnson Syndrome (SJS) necessitates cautious therapeutic assessment. While the development of SJS has generally been associated with high starting dosages, renal impairment, and the presence of pharmacogenetic markers such as HLA-B*58:01,

International Journal of Pharmaceutical research and Applications
Volume 10, Issue 3, May-June 2025, pp:1003-1007 www.ijprajournal.com ISSN: 2456-4494

this case report demonstrates that major adverse effects can occur with low-dose therapy and in the absence of recognized risk factors.

The current case highlights the unpredictable nature of idiosyncratic medication reaction and underscores the vital need of keeping a high level of suspicion during the first few weeks of allopurinol therapy. Early detection of cutaneous and systemic symptoms of SJS, such as erythema, blistering, fever, and malaise, is critical for preventing disease development and lowering morbidity and mortality. Immediate withdrawal of the offending medication remains the cornerstone of treatment, along with supportive measures such as fluid replenishment, wound care, corticosteroids, and antimicrobial therapy if needed.

Furthermore, this example demonstrates the difficulties of depending simply on identified risk indicators to ensure safe prescribing. It supports the rising international recommendation for preemptive HLA-B*58:01 screening, particularly in genetically susceptible populations, while simultaneously recommending for increased clinical vigilance in all patient groups, independent of ethnicity or baseline renal function. Long-term risk mitigation requires comprehensive documentation of drug sensitivities, patient education, and the identification of medical alerts. Finally, this case emphasizes the importance of tailored medication, pharmacovigilance, and additional research into predictive biomarkers and safer pharmacological alternatives in gout care to reduce the likelihood of severe adverse drug responses.

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