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Informe de caso clínico

Allopurinol-Induced Toxic Epidermal Necrolysis: Diagnostic and Therapeutic Challenges

Necrólisis Epidérmica Tóxica Inducida por Alopurinol: Retos diagnósticos y terapéuticos

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ABSTRACT

We report the case of a 54-year-old male who developed a severe and widespread cutaneous adverse reaction consistent with toxic epidermal necrolysis (TEN) one week after initiating allopurinol treatment for gout. This case contributes to the medical literature by expanding knowledge on the clinical presentation, diagnostic challenges, and therapeutic management of allopurinol-induced TEN. The patient exhibited an extensive skin rash, blistering, and epidermal detachment affecting approximately 70 % of his body surface area, along with mucosal involvement and systemic complications including acute kidney injury and electrolyte disturbances. Diagnosis was established based on clinical and histopathological findings and supported by a high ALDEN score of 10, indicating a probable drug causality. Management focused on intensive supportive care, pain control, infection prevention, and immediate discontinuation of allopurinol. Despite aggressive treatment, the patient had a prolonged recovery course complicated by secondary infections and required adjustments in antimicrobial therapy. This case underscores the importance of early recognition and multidisciplinary intervention in TEN, as well as the need for awareness regarding severe cutaneous adverse reactions associated with commonly prescribed drugs such as allopurinol.

KEY WORDS: Toxic epidermal necrolysis, Stevens-Johnson syndrome, drug eruptions, allopurinol, case report.

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RESUMEN

Se presenta el caso de un paciente de 54 años que desarrolló una reacción cutánea grave y generalizada conocida como necrólisis epidérmica tóxica (TEN) tras una semana después de iniciar tratamiento con alopurinol para la gota presentando una evolución clínica complicada. El presente reporte de caso contribuye a la literatura médica al ampliar el conocimiento sobre la presentación clínica, el diagnóstico y el manejo de la TEN inducida por alopurinol. Al detallar las características clínicas, los hallazgos histopatológicos y la respuesta al tratamiento en un paciente específico. El paciente experimentó una erupción cutánea extensa, ampollas y desprendimiento de la piel, afectando aproximadamente el 70 % de su cuerpo. Además, presentó complicaciones sistémicas como insuficiencia renal y alteraciones electrolíticas. El diagnóstico se confirmó mediante hallazgos clínicos, histopatológicos y una puntuación de 10 en la escala ALDEN. El tratamiento se centró en medidas de soporte vital, control del dolor y prevención de infecciones, así como en la suspensión inmediata del alopurinol. A pesar del tratamiento intensivo, el paciente presentó una recuperación lenta, complicaciones infecciosas secundarias y requerimientos de ajuste terapéutico.

PALABRAS CLAVE: Necrólisis epidérmica tóxica, síndrome de Stevens-Johnson, erupciones por medicamentos, alopurinol, reporte de caso.

Introduction

Toxic epidermal necrolysis (TEN), also referred to as Lyell's syndrome, and Stevens-Johnson syndrome (SJS) are severe adverse drug reactions. Although initially described as distinct entities, they are now considered variants within the same pathological spectrum, differing only in severity (Broyles *et al*., 2020; Heng *et al*., 2015; Lissia *et al*., 2010). SJS/TEN are rare disorders, but their overall mortality is significantly estimated at 23 % at six weeks and up to 34 % at one year (95 % CI: 30–39 %) (Stamp & Chapman, 2020).

TEN is characterized by widespread epidermal detachment affecting more than 30 % of the total body surface area, which distinguishes it from SJS, where detachment involves less than 10 % (Sekula *et al*., 2013). Clinically, TEN manifests with vesicle formation and extensive skin exfoliation, often presenting with a positive Nikolsky sign, laminar detachment of the epidermis induced by lateral pressure on the skin resembling second-degree burn injuries (Cid Conde *et al*., 2009).

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Among the many drugs identified as potential triggers of TEN, allopurinol is one of the most frequent culprits. Widely used for the management of hyperuricemia due to its efficacy, low cost, and favorable adherence, allopurinol has been associated with a spectrum of hypersensitivity reactions ranging from mild maculopapular eruptions to rare and life-threatening events like TEN (Anis & Meher, 2023; Perdigão *et al*., 2024; Stamp *et al*., 2016). The pathogenic mechanism of allopurinol-induced TEN involves a T-cell-mediated immune response that leads to keratinocyte apoptosis. The presence of the HLA-B*58:01 allele has been linked to an increased risk of developing this adverse reaction (Ferdiana *et al*., 2022). Currently, there is no targeted treatment for TEN, and supportive care remains the cornerstone of management (Stamp & Chapman, 2020).

Although recent advances have improved the prognosis of TEN, there is still a lack of comprehensive global epidemiological data on mortality and prevalence specifically related to allopurinol-induced TEN. Despite being classified as a rare, severe cutaneous adverse reaction (SCARs), the morbidity and mortality potential of this condition justify rigorous clinical monitoring (Broyles *et al*., 2020). This case report makes a valuable contribution to the medical literature by detailing the clinical features, histopathological findings, and treatment response in a patient with allopurinol-induced TEN, offering insights that may assist clinicians in early recognition and effective management of this critical condition.

Material and Methods

This case report was conducted under the CARE (CAse REport) Guidelines, using a retrospective and systematic collection of clinical, therapeutic, and follow-up information extracted from the institutional electronic medical record. The case involves a 54-year-old male with a history of methamphetamine use who developed toxic epidermal necrolysis (TEN) one week after initiating treatment with allopurinol at a dose of 100 mg/day. As detailed in Table 1, the initial presentation included a pruritic skin rash that rapidly progressed to epidermal necrolysis, affecting approximately 70 % of the total body surface area, predominantly involving the trunk and extremities. Erosive lesions were also observed on the oral, ocular, and genital mucosae.

At hospital admission, the patient exhibited asthenia, adynamia, hyporexia, and generalized pruritus. Physical examination revealed diffuse erythema, flaccid blisters, extensive epidermal detachment, and a positive Nikolsky sign. The oral and ocular mucosae showed erosive and desquamative lesions. Laboratory tests revealed leukopenia (3,500 cells/μL), thrombocytopenia (45,000 platelets/μL), acute kidney injury (creatinine 2.31 mg/dL, urea 89.7 mg/dL), metabolic acidosis (pH 7.33, HCO_3^- 13.7 mmol/L), and hyponatremia with hypochloremia.

The diagnosis of TEN was established based on clinical criteria (extensive skin lesions, positive Nikolsky sign, and mucosal involvement) and confirmed by skin biopsy demonstrating epidermal necrosis. The causative relationship with allopurinol was supported by an ALDEN score of 10, indicating a very probable drug-induced etiology.

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Table 1. Clinical Evolution of a Case of Allopurinol-Induced TEN.

Period	Clinical Findings	Complementary Tests	Treatment	Evolution/ Response	Notes/ Observations
Start	Pruritic maculopapular rash.	-	Allopurinol 100 mg/day.	-	Start of treatment with allopurinol.
Day 1	Extension of the rash, onset of blister formation.	-	Allopurinol discontinuation.	Initial progression of the rash.	Onset of adverse reaction.
Day 2-5	Extension of the rash, blister formation, 70 % BSA involvement, mucosal lesions (oral, ocular, genital).	Leukopenia, thrombocytopenia (67 x 10^3/µL), acute renal failure (creatinine 2.31 mg/dL, BUN 42 mg/dL), metabolic acidosis (pH 7.33, HCO3 13.7 mmol/L, pCO2 26 mmHg), electrolyte imbalances (Na 123 mmol/L, K 3 mmol/L, Cl 91.9 mmol/L).	Ketorolac 30 mg IV q6h, Tramadol 100 mg IV in 100 cc NaCl 0.9 %, Ceftriaxone 1 g IV q12h, Silver sulfadiazine, Hypromellose drops 1 in each eye q4h.	Rapid progression of lesions, systemic involvement.	Diagnosis of TEN.
Day 6-12	Extensive epidermal detachment, positive Nikolsky's sign, crust formation.	Improvement of inflammatory and coagulation parameters.	Hydrocortisone 300 mg IV q8h, IV immunoglobulin (0.2 mL/kg/day for 5 days), Buprenorphine 600 mcg in 100 cc D5W over 24h, Cefepime 1 g IV over 24h, 1 % Gentian violet twice daily.	Partial stabilization of lesions, onset of healing.	Start of corticosteroid and immunoglobulin therapy.
Day 13 onwards	Progressive healing, secondary bacterial infection.	-	Ceftazidime 1 g IV q12h, Cefepime 1 g IV q8h, outpatient follow-up.	Progressive resolution of lesions, general clinical improvement.	Antibiotic adjustment for secondary infection, start of outpatient follow-up.

Description: The following table details the clinical evolution of a patient diagnosed with allopurinol-induced toxic epidermal necrolysis (TEN), from the onset of symptoms to hospital discharge. It presents the most relevant clinical findings, the results of complementary tests, the treatment initiated at each stage, and its evolution.

Source: Own elaboration based on the patient's clinical records, documented medical data, and therapeutic course during hospitalization.

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Treatment was initiated immediately following the diagnosis of TEN, with the primary goal of halting lesion progression, controlling symptoms, and preventing complications. The first critical step was the immediate discontinuation of allopurinol, the drug identified as the causative agent of the adverse reaction. This measure is essential to eliminate further exposure and prevent additional damage.

Between days 2 and 5, the patient experienced rapid lesion progression, with involvement of 70 % of the total body surface area and mucosal compromise. To manage the intense pain associated with the lesions, ketorolac was administered intravenously at a dose of 30 mg every 6 hours, and tramadol at 100 mg intravenously in 100 mL of 0.9 % NaCl. Given the high risk of secondary infection due to extensive loss of the skin barrier, intravenous ceftriaxone 1 g every 12 hours was initiated. Silver sulfadiazine was applied topically to treat the extensive skin lesions. In addition, hypromellose eye drops were administered every 4 hours to protect the ocular mucosa.

From days 6 to 12, the patient showed extensive epidermal detachment and a positive Nikolsky sign, indicating a critical phase of the disease. However, inflammatory and coagulation markers began to improve, suggesting a favorable response to treatment. Therapy was intensified with intravenous hydrocortisone at a dose of 300 mg every 8 hours to modulate the systemic inflammatory response. Intravenous immunoglobulin (IVIG) was administered at a dose of 0.2 mL/kg/day for 5 days to inhibit the autoimmune reaction and limit disease progression.

The rationale for IVIG use in TEN lies in its ability to modulate the immune response and mitigate the severity of the hyperimmune cutaneous reaction. The combination of IVIG and systemic corticosteroids has shown favorable outcomes in TEN and other severe adverse drug reactions. Previous studies support this approach, reporting complete resolution in TEN cases treated with this combination, even in patients with polypharmacy (Barrera-Ochoa *et al*., 2022).

For management of severe pain, buprenorphine was administered at a dose of 600 mcg in 100 mL of glucose solution via intravenous infusion over 24 hours. Prophylactic antibiotic coverage was maintained with cefepime 1 g IV every 24 hours. For mucosal lesion care, 1 % gentian violet was applied twice daily, resulting in partial stabilization of the lesions and the initiation of re-epithelialization. No adverse drug reactions were observed with any of the therapeutic agents used.

Results and Discussion

The patient was closely monitored to assess therapeutic response and disease progression. By day 13, progressive re-epithelialization of the lesions was observed. However, the patient developed a secondary bacterial infection, characterized by extensive epidermal detachment and blister formation, which required adjustment of the antibiotic regimen. Intravenous ceftazidime (1 g every 12 hours) was initiated, and the dose of cefepime was increased to 1 g every 8 hours. Following the therapeutic adjustment, gradual clinical improvement was noted, with decreased erythema and crust formation, indicative of ongoing skin healing.

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Given the overall clinical improvement reflected in reduced pain and pruritus as reported by the patient, weekly outpatient follow-up was recommended during the first month, including hematological and biochemical monitoring, as well as the use of emollients and protective dressings. Nevertheless, due to the severity of TEN and the presence of acute kidney injury, the patient faces an unfavorable prognosis, with a high risk of developing chronic skin sequelae, long-term renal complications, and a significant impact on quality of life. Therefore, prolonged and close follow-up is strongly recommended to identify and manage potential late complications.

This clinical case underscores the critical importance of early diagnosis and aggressive management in drug-induced TEN. Immediate withdrawal of the offending agent, in combination with systemic corticosteroids and intravenous immunoglobulin (IVIG), constitutes the cornerstone of treatment to improve outcomes (Kridin *et al*., 2021). However, the occurrence of complications such as secondary infections highlights the need for close monitoring and a multidisciplinary approach.

TEN is primarily caused by altered drug metabolism, triggering a dose-independent immune reaction (Hasegawa & Abe, 2020). This autoimmune response leads to widespread epidermal detachment. With an incidence of 2 to 13 cases per million people, TEN is a rare condition, with sepsis being the leading cause of mortality (Tunuguntla *et al*., 2023).

In the case of allopurinol, the underlying mechanism is believed to involve immunoallergic hypersensitivity to its main metabolite, oxypurinol (Anis & Meher, 2023). This reaction results in epidermal separation, manifesting as blisters and laminar detachment, generating large areas of denuded skin. The disease typically begins on the face and trunk and then spreads to the extremities, presenting with characteristic maculopapular rashes and exfoliative dermatitis (Kim *et al*., 2021; Wakamatsu *et al*., 2021).

Symptoms usually appear within the first week of treatment initiation (Edinoff *et al*., 2021). Presentation of TEN affecting more than 30 % of the body surface, as in this case, is uncommon and often associated with severe systemic complications such as acute kidney injury, electrolyte imbalance, and bicytopenia, requiring intensive management (Perdigão *et al*., 2024).

Current treatment focuses on prompt withdrawal of the causative drug and supportive care similar to that provided for burn patients, with emphasis on sepsis prevention (Hoyer *et al*., 2021). The efficacy of high-dose IVIG remains controversial, with some studies reporting benefits while others find no significant advantage over corticosteroids alone (Kridin *et al*., 2021).

The presence of the HLA-B*58:01 allele has been associated with an increased risk of allopurinol-induced TEN, suggesting that genetic screening may play a valuable role in prevention (Ferdiana *et al*., 2022). Biological therapies, such as TNF-α inhibitors, are being explored for refractory cases (Nikitina *et al*., 2023).

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This case is notable for its detailed documentation of management and follow-up, contributing to the understanding of allopurinol-induced TEN. However, limitations include the absence of clinical photographs and long-term follow-up data.

Conclusions

This case highlights the importance of early and accurate diagnosis, as well as the complexity of managing allopurinol-induced toxic epidermal necrolysis (TEN). It underscores the need for an individualized, multidisciplinary approach. The identification of genetic risk factors may play a critical role in preventing this severe adverse drug reaction.

Author Contributions

Author 1: Case conceptualization, clinical supervision, data collection, original manuscript drafting, critical intellectual content review, project management, and journal submission. Principal responsibility for clinical follow-up, histopathological interpretation, and design of the clinical course table. Author 2: Literature review, reference management, support in drafting the introduction and discussion sections, grammar review, and manuscript editing, and collaboration on the clinical course table. Author 3: Participation in clinical documentation, data analysis, initial drafting of the abstract in Spanish and English, and assistance with table formatting and reference style compliance. Author 4: Co-design of the manuscript's narrative structure, support in drafting the therapeutic and clinical findings sections, validation of consistency between clinical findings and treatment, final review for compliance with CARE guidelines. Author 5: Assistance with literature search on allopurinol and adverse drug reactions, contribution to English translation of the manuscript, critical review, and suggestions to enhance scientific clarity.

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Informed Consent Statement

In this clinical case, written informed consent could not be obtained due to the rapid disease progression and the imminent threat to the patient's life. Nevertheless, full data anonymization was ensured, and all actions were in compliance with the ethical principles of the Declaration of Helsinki. This decision was duly documented in the patient's medical record. Patient data were completely anonymized to safeguard privacy, following international standards.

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Conflict of Interest

The authors declare no conflicts of interest related to this research. Furthermore, the authors have no personal, financial, or professional relationships that could compromise the objectivity of this report.

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