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Case Report

DRESSed for Distress: A Case of Allopurinol-Induced DRESS Syndrome

Areti Kalfoutzou[1], Aikaterini Doumana[2], Aimilia-Iris Karamolegkou[2], Adam Mylonakis[3], Christos Piperis[4], Maria Dimitrakoudi[5], Eleni Mostratou[2]

[1] *Department of Oncology, 251 Air Force General Hospital, Athens, Greece*

[2] *Second Department of Internal Medicine, 251 Air Force General Hospital, Athens, Greece*

[3] *First Department of Surgery, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece*

[4] *Department of Cardiology, Georgios Gennimatas General Hospital, Athens, Greece*

[5] *Department of Hematology, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece*

Corresponding author: Areti Kalfoutzou, Department of Oncology, 251 Air Force General Hospital, Athens, Greece; Email: aretik92@gmail.com

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Abstract

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome is a severe systemic drug reaction characterized by a latent period of several weeks following the initiation of drug therapy. Among the most well-known causative agents is allopurinol, commonly prescribed for managing asymptomatic gout. Allopurinol-induced DRESS syndrome is associated with high mortality rates and significant long-term sequelae. This report details the case of an elderly female patient who presented with an extensive rash covering her trunk and extremities which was concurrent with her use of allopurinol. The condition progressed to renal impairment but showed significant improvement upon cessation of the drug and administration of high-dose corticosteroids. This case aims to shed light on one of the most underrecognized types of systemic drug reactions, hoping to raise awareness about this rare yet serious complication of one of the most widely prescribed drugs.

Keywords

allopurinol, corticosteroids, eosinophilia, hypersensitivity

INTRODUCTION

Allopurinol is a xanthine oxidase inhibitor effectively used in the management of hyperuricemia by impeding uric acid synthesis.[1] This drug, however, can also precipitate a specific type of multi-organ drug reaction known as allopurinol-induced DRESS syndrome, which has a reported incidence of 0.4%.[2,3] Typically presenting with fever and an extensive maculopapular rash and mucosal involvement, this condition manifests between 2 to 6 weeks after commencing allopurinol treatment.[4,5] It frequently impacts the kidneys, liver and lungs, potentially leading to permanent organ failure.[6,7] In this report, we describe a case involving a 75-year-old woman who developed a maculopapular rash and perioral skin peeling four weeks following the initiation of allopurinol. The condition progressed to renal impairment but significantly improved following the cessation of the culprit drug and the administration of high-dose corticosteroids. This case emphasizes the importance of careful patient selection for allopurinol treatment, expands on the various presentations of allopurinol-induced DRESS syndrome, and raises awareness for early recognition of this condition.

CASE PRESENTATION

A 75-year-old female patient presented to the Emergency Department with a five-day history of a non-pruritic persistent

rash. Her medical history included arterial hypertension, cardiac failure with a reduced ejection fraction (EF 35%), and hypothyroidism. The patient was prescribed the following medications: levothyroxin, furosemide, losartan, and metoprolol. Additionally, the patient had started therapy with allopurinol at a dosage of 100 mg daily four weeks prior for managing asymptomatic hyperuricemia. Clinical examination revealed bilateral cervical lymphadenopathy and a non-blanching maculopapular rash on the trunk and extremities. Involvement of the oral mucosa with perioral desquamation was observed, as well as mild periorbital edema. The patient was afebrile (36.8°C), well-oriented in time and space, and neurologic examination was within normal limits ***(Fig. 1)****.*

Laboratory examinations showed mild leukocytosis with a neutrophil predominance and impaired kidney function (patient's baseline creatinine: 1.2 mg/dL) ***(Table 1)****. Blood cultures as well as tests for Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis viruses (including hepatitis A, B, and C), and human immunodeficiency virus (HIV) were all negative. A full antibody panel, including antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and antimitochondrial antibodies (AMA), was within normal limits. The patient was admitted for further evaluation, and the initial rash progressed to perioral and palmar desquamation over the following days.*

Among the wide range of differential diagnoses considered were bacterial infection, systemic drug reaction, Kawasaki disease, and paraneoplastic syndrome. Allopurinol was suspected as the culprit of the skin manifestations, leading to its immediate discontinuation. The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score was calculated at 5, categorizing the diagnosis of allopurinol-induced DRESS syndrome as probable ***(Table 2)****.*

Treatment with methylprednisolone at a dose of 1 mg/kg daily was initiated, leading to significant improvement of the rash and desquamation within two weeks, and normalization of kidney function within three weeks. The patient's hospital stay was complicated by episodes of worsening dyspnea, managed with fluids, diuretics, and continued steroid therapy. She was discharged on a slow taper of methylprednisolone over two months and reported complete resolution of symptoms at her three-month follow-up visit. She remains under close

Table 1. Patient's laboratory examinations upon admission

Laboratory examination	Patient's values	Normal Range
White blood cells (WBC)	**13.4**	4–10 K/μL
Neutrophils	**11.4**	1.5–7 K/μL
Lymphocytes	**7**	20–45 K/μL
Eosinophils	0.1	0–0.7 K/μL
Urea	**209**	15–54 mg/dL
Creatinine	**2.22**	0.55–1.2 mg/dL
ALT	**35**	5–40 IU/L
AST	**26**	5–45 IU/L
Bilirubin (total)	0.9	0.1–1.3 mg/dL
Bilirubin (direct)	0.2	0–0.3 mg/dL
Potassium	3.8	3.5–5.3 mEq/L
Sodium	135	137–150 mEq/L

ALT: alanine aminotransferase, AST: aspartate aminotransferase

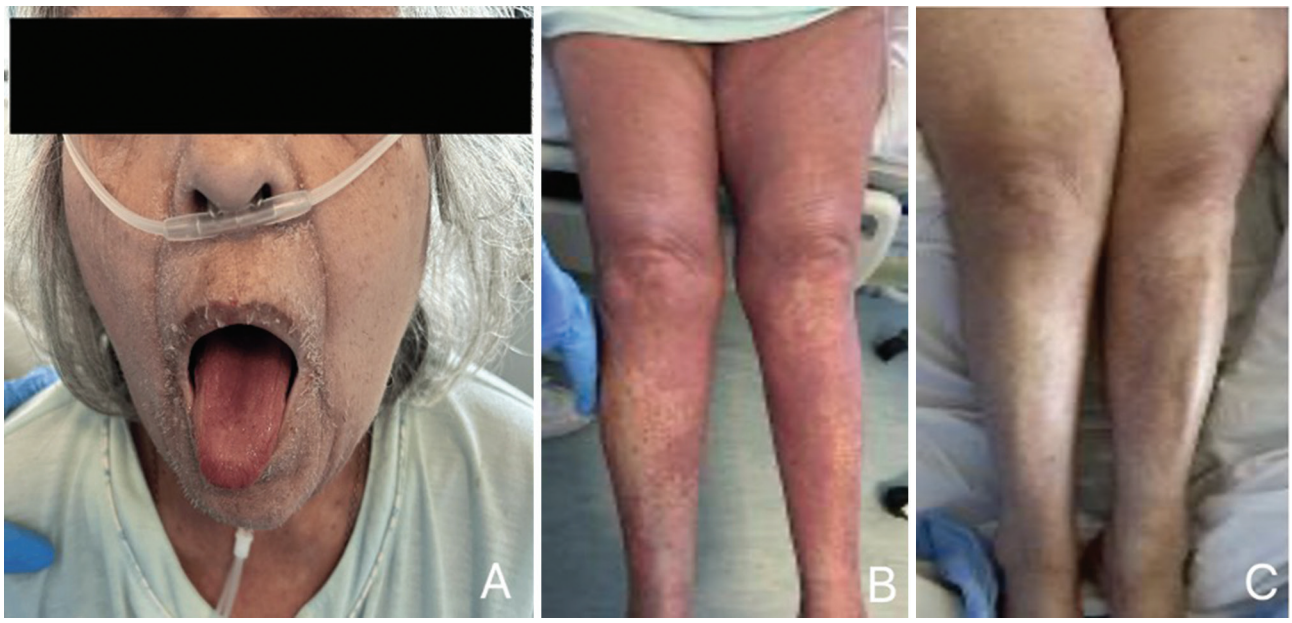

Figure 1. **A**: Pronounced perioral desquamation is depicted, characterized by prominent peeling and flaking of the skin around the mouth; **B**: A maculopapular rash extensively affects the lower extremities, showing widespread coverage; **C**: Two weeks post-presentation – there is marked improvement in the skin condition, demonstrating significant healing.

Table 2. RegiSCAR group scoring system for diagnosing DRESS syndrome in hospitalized patients[19]

Criteria	Score			
	-1	0	1	2
Fever ≥38.5°C	No	Yes		
Enlarged lymph nodes		No/U	Yes	
Eosinophilia			700-1499	≥1500
Eosinophils, if lymphocytes are <4000			10-19%	≥20%
Atypical or reactive lymphocytes		No/U	Yes	
Rash covering ≥50% of body surface area		No/U	Yes	
Suspicious rash (≥2 facial edema, purpura, infiltration, desquamation)	No	U	Yes	
Skin biopsy suggesting an alternative diagnosis	No	Yes/U		
Organ involvement:		No/U		
Lung manifestations			Yes	
Hepatic impairment			Yes	
Kidney impairment			Yes	
Pancreatic impairment			Yes	
Heart/muscle manifestations			Yes	
Other organ involvement			Yes	
Disease duration >15 days	No/U	No/U		
Investigation of 3 or more alternative causes (blood cultures, anti-nuclear antibody, serology for hepatitis viruses, mycoplasma, chlamydia) with negative results			Yes	

*U: unknown; Final score: <2 (negative case), 2 to 3 (possible case), 4 to 5 (probable case), and >5 (definitive case)

monitoring for hyperuricemia, with plans to initiate febuxostat if gout symptoms occur.

DISCUSSION

DRESS syndrome, also known as Drug-Induced Hypersensitivity Syndrome (DIHS), is a severe systemic reaction characterized by a rash, fever, lymphadenopathy, and multiorgan involvement.[6,8,9] Common culprits include non-steroid anti-inflammatory drugs (NSAIDs), sulphonamides, antibiotics, anticonvulsants, and notably, allopurinol.[8,10]

Allopurinol, a xanthine oxidase inhibitor, is primarily used to reduce uric acid levels in patients with gout and chronic kidney disease.[11] While generally effective, adverse reactions occur in up to 8% of patients, ranging from mild skin rashes to severe conditions like Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS syndrome.[11] The incidence of allopurinol-induced DRESS syndrome is approximately 1 in 260 patients.[1,8]

The pathogenesis of allopurinol-induced DRESS syndrome involves a complex interplay of genetic predispositions, immune system dysregulation, and drug metabolism.[6,8,11-14] A key genetic factor is the presence of the HLA*B5801 allele, which is particularly prevalent among patients of Asian descent, correlating with a higher risk of the syndrome.[6] In fact, a study by Sornsamdang et al. proved a statistically significant association between the HLA-B*58:01 allele and allopurinol-induced cutaneous drug reactions in Thai patients.[15] A familial predisposition to DRESS syndrome has also been reported, suggesting a heritable component to immune system responsiveness.[16] Metabolically, the condition involves the accumulation of oxypurinol, a metabolite of allopurinol, especially in patients with renal impairment, which can potentiate immune dysregulation.[6] Additionally, DRESS syndrome may be triggered by an initial immune response to the drug or its metabolites, followed by a delayed hypersensitivity reaction involving reactivation of latent herpesviruses.[6,16,17]

The clinical presentation is often atypical and begins 2-6 weeks after drug initiation.[4,5] It usually begins with fever, fatigue, and a maculopapular rash that starts on the face and spreads, often accompanied by facial or periorbital edema.[4,5,8] Involvement of the oral mucosa is common, and multi-system manifestations may affect any organ, including the liver, kidneys, lungs, heart, central nervous system, and endocrine glands.[4,6]

Diagnosis of DRESS syndrome is often challenging due to the long latency period, atypical clinical presentation, and multi-system involvement.[1] A thorough history linking symptom onset to drug initiation is crucial.[6] Laboratory tests usually reveal leukocytosis, atypical lymphocytosis, eosinophilia, and thrombocytopenia, while biochemical

tests often show elevated liver function tests and acute kidney injury.[4,8,14,17] Skin biopsy demonstrating a lymphocytic reaction, along with patch testing, can offer definitive diagnostic insights.[6,9]

Multiple diagnostic tools have been developed to facilitate diagnosis of DRESS syndrome. The criteria created by Bocquet et al. in 1996 still hold clinical utility in diagnosing DRESS syndrome.[18] According to Bocquet's criteria, the diagnosis requires at least three of the following: skin eruption, hematologic abnormalities such as eosinophilia (>1.5×10^9/L) or the presence of atypical lymphocytes, systemic involvement indicated by lymphadenopathies (>2 cm in diameter), hepatitis (liver transaminase levels >2 times the normal), interstitial nephritis, interstitial pneumonitis, or carditis.[18] Furthermore, a more recent set of criteria established by the Japanese group for diagnosing DIHS include the following: maculopapular rash developing more than three weeks after starting a limited number of drugs, prolonged clinical symptoms two weeks after discontinuing the causative drug, fever over 38°C, elevation of liver enzyme (ALT >100 U/L) or involvement of other organs, leukocytosis (>11×10^3/μL), atypical lymphocytosis (>5%) or eosinophilia (>1.5×10^3/μL), lymphadenopathy, and human herpesvirus (HHV)-6 reactivation.[18] Diagnosis of typical DIHS requires the presence of all seven criteria.[18] Currently, the RegiSCAR group score is the most widely used in clinical practice, utilizing clinical and laboratory criteria to categorize DRESS syndrome diagnosis as definite, probable, possible, or impossible **(Table 2)**.[19] Differential diagnosis includes various types of drug reactions and diseases that involve both skin and systemic symptoms, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, hypereosinophilic syndrome, Still's disease, and Kawasaki disease, among others.[1,8,16]

Treatment cornerstones are the immediate cessation of the offending drug and the early initiation of systemic corticosteroids, such as prednisolone at a dose of 0.5-2 mg/kg daily, with gradual tapering to avoid recurrences.[8,9] Topical corticosteroids are used for milder cases, and supportive measures such as fluid resuscitation, anti-histamines and antipyretics are crucial.[4] For severe cases associated with viral reactivation, intravenous immunoglobulin (IVIG) may be administered.[5] Allopurinol can be reintroduced at lower doses following a specific desensitization protocol if deemed necessary.[1,8,13]

Allopurinol-induced DRESS syndrome can be fatal, with a reported mortality rate exceeding 25%.[14] Poor prognostic factors include an eosinophil count above 6000×10^3/mL, thrombocytopenia, pancytopenia, leukocytosis and coagulopathy.[6] Fulminant liver or kidney failure, sepsis, or gastrointestinal bleeding are some of the reported causes of death in these patients.[14]

It is estimated that up to 80% of patients with allopurinol-induced DRESS syndrome were initially treated for asymptomatic hyperuricemia.[1] Advanced age and compromised renal function or concurrent use of thiazide diuretics increase the risk.[19] This highlights the need for healthcare professionals to judiciously assess the risk versus benefit of allopurinol, considering individual patient factors and renal function, to ensure safety and effectiveness.

CONCLUSION

Allopurinol-induced DRESS syndrome is a potentially fatal condition that necessitates careful risk assessment before prescribing, particularly for patients with asymptomatic hyperuricemia and those at increased risk due to age or renal dysfunction. Collaboration with a dermatologist is essential for early recognition and management, as prompt identification and discontinuation of the offending drug are critical to preventing severe outcomes and ensuring patient safety.

Author contribution

All authors have accepted responsibility for the entire content of this submitted manuscript and approved its submission. A.K. conceptualized the study, led the data interpretation, and drafted the initial manuscript. AD and A.-I.K. were involved in data collection and critical revision of the manuscript for important intellectual content. A.M. contributed to the study design and performed the statistical analysis. C.P. participated in data collection and analysis and assisted in drafting the manuscript. M.D. provided substantial contributions to the conception of the work and revised it critically for important intellectual content. E.M. assisted in data collection, contributed to manuscript preparation, and reviewed the final version of the manuscript.

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Conflict of Interest

Authors state no conflict of interest.

Informed consent

Informed consent has been obtained from the patient included in this study.

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DRESS синдром и дистресс: случай синдрома DRESS, вызванного аллопуринолом

Арети Калфуцу[1], Айкатерини Думана[2], Аимилия-Ирис Карамолегку[2], Адам Милонакис[3], Христос Пиперис[4], Мария Димитракуди[5], Елени Мострату[2]

[1] *Отделение онкологии, 251-ый госпиталь ВВС, Афины, Греция*

[2] *Второе отделение внутренних болезней, 251-ый госпиталь ВВС, Афины, Греция*

[3] *Первое хирургическое отделение, Национальный Афинский университет имени Каподистрии, Больница „Лаикон", Афины, Греция*

[4] *Отделение кардиологии, Больница „Георгиос Гениматас", Афины, Греция*

[5] *Кафедра гематологии, Национальный Афинский университет имени Каподистрии, Больница „Лаикон", Афины, Греция*

Адрес для корреспонденции: Арети Калфуцу, Отделение онкологии, 251-ый госпиталь ВВС, Афины, Греция, Email: aretik92@gmail.com

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Резюме

Синдром DRESS (реакция на лекарственные препараты с эозинофилией и системными симптомами) – это тяжёлая системная лекарственная реакция, характеризующаяся латентным периодом в несколько недель после начала лекарственной терапии. Среди наиболее известных возбудителей – аллопуринол, обычно назначаемый для лечения бессимптомной подагры. Синдром DRESS, вызванный аллопуринолом, связан с высокими показателями смертности и значительными долгосрочными последствиями. В этом отчёте подробно описывается случай пожилой пациентки с обширной сыпью, покрывающей её туловище и конечности, которая сопровождалась приёмом аллопуринола. Состояние прогрессировало до почечной недостаточности, но показало значительное улучшение после прекращения приёма препарата и введения высоких доз кортикостероидов. Цель этого случая – пролить свет на один из самых недооценённых типов системных лекарственных реакций, надеясь повысить осведомлённость об этом редком, но серьёзном осложнении одного из наиболее широко назначаемых препаратов.

Ключевые слова

аллопуринол, кортикостероиды, эозинофилия, гиперчувствительность