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CASE REPORT

ALLOPURINOL-INDUCED DRESS SYNDROME IN A CASE OF RENAL INSUFFICIENCY

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ABSTRACT

Introduction: Allopurinol, a xanthine oxidase inhibitor, is widely prescribed in cases of gout and hyperuricosuria. Notably, allopurinol is not recommended in the case of asymptomatic hyperuricemia. Despite its efficacy, it carries the risk of rare but severe hypersensitivity reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome which is characterised by fever, rash, facial oedema, eosinophilia, and multiorgan involvement, typically emerging 2–8 weeks after drug initiation. **Case Presentation:** A 63-year-old female with a history of hypertension and chronic kidney disease presented to Dermatology OPD with a 10-day history of generalised morbilliform rash, pruritus, and facial oedema. These symptoms developed 1 month after initiating allopurinol for asymptomatic hyperuricemia. On examination, skin lesions were present on the trunk and extremities as morbilliform eruptions along with desquamation of skin over face and back, and systemic manifestations. Laboratory results revealed leukocytosis, marked eosinophilia, elevated pancreatic enzymes impaired hepatic and renal function tests. A diagnosis of allopurinol-induced DRESS syndrome was made. Allopurinol was discontinued, and the patient was treated with systemic corticosteroids and supportive care. Clinical and biochemical parameters improved over 21 days, and corticosteroids were tapered over 2 months. The causality assessment using the WHO scale classified the reaction as "Probable/Likely." **Conclusion:** This case highlights the development of DRESS syndrome following allopurinol ingestion in a 63-year-old female with renal insufficiency. Our case underscores the need for heightened awareness of drug toxicity reactions in geriatric patients receiving allopurinol. Allopurinol-induced DRESS syndrome carries a high risk of mortality, so caution is essential while prescribing this drug as well as careful consideration of the co-morbidities and associated risk factors.

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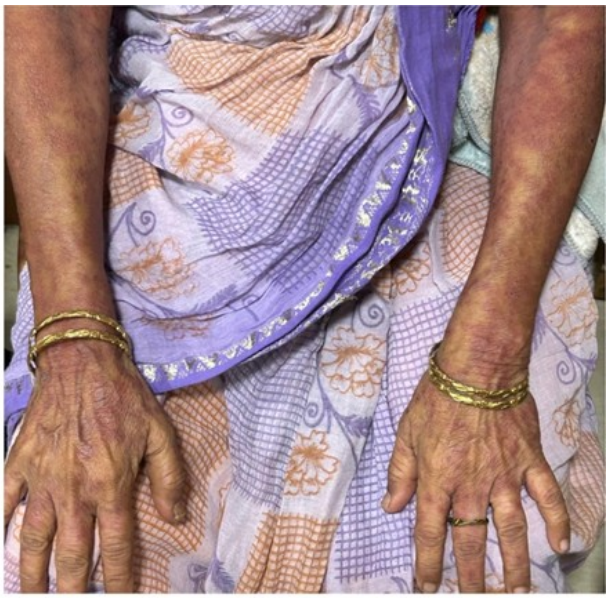
INTRODUCTION

Allopurinol, a xanthine oxidase inhibitor, acts by inhibiting uric acid synthesis and is approved by the FDA for the management of gouty arthritis, prevention of recurrent calcium nephrolithiasis in hyperuricosuric patients and prevention of tumour lysis syndrome. Notably, allopurinol is not recommended in the case of asymptomatic hyperuricemia[1]. Allopurinol is poorly tolerated in some patients and sometimes may lead to idiosyncratic drug reactions. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare, severe, unpredictable adverse reaction to a drug characterised by delayed onset of symptoms. DRESS syndrome consists of a wide range of clinical manifestations typically emerging 2 to 8 weeks after initiating the offending drug. Its incidence is 1/1000 to 1/10000 drug exposure without any gender predilection. Patients with DRESS syndrome present with fever, generalised rash, facial oedema, lymphadenopathy, abnormal haematological profile (eosinophilia, leukocytosis, atypical lymphocytosis), deranged liver function tests, and renal dysfunction[2]. A broad spectrum of medications is associated with DRESS including antibiotics, anticonvulsants, allopurinol, and sulphonamides.

CASE PRESENTATION: A 63-year-old female presented to Dermatology OPD with a history of skin rash, fever, pruritus, and facial puffiness for 10 days. The skin rash first appeared on the trunk, which later spread to the face and the upper and

lower extremities bilaterally within 4 days. She had a 15-year history of hypertension and stage 2 chronic kidney disease (estimated GFR 70mL/min/1.73m^2). Her medications included amlodipine 5 mg per day and calcium 500 mg + vitamin D3 250 IU. Allopurinol for hyperuricemia, 100 mg per day, was started 1 month back for management of asymptomatic hyperuricosuria. The patient was afebrile with pallor, blood pressure 150/70 mm Hg, pulse 112 beats/min, and respiratory rate 18 breaths/min without lymphadenopathy. On physical examination, palpable skin lesions were present on the trunk and extremities as morbilliform eruptions along with involvement of oral mucosa, tongue, and palate (see Fig. 1). Desquamation of skin over the face, perioral area and back was noticed (see Fig. 2).



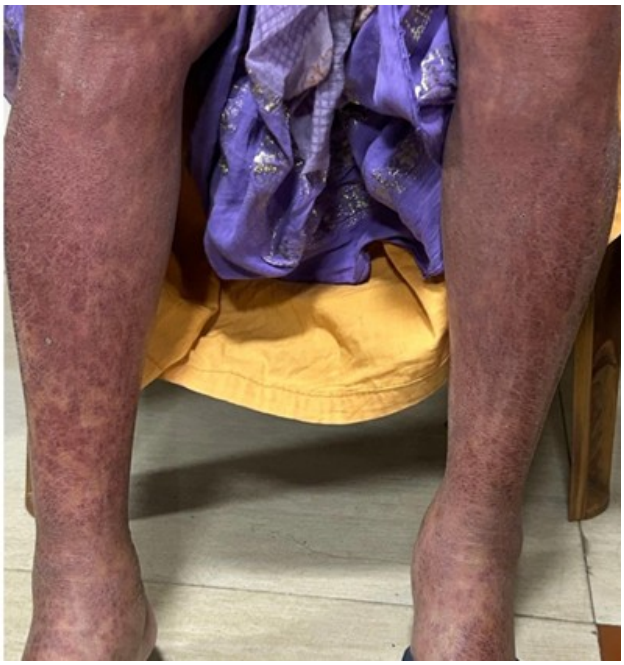


Fig. 1. Morbilliform rash on upper and lower extremities.

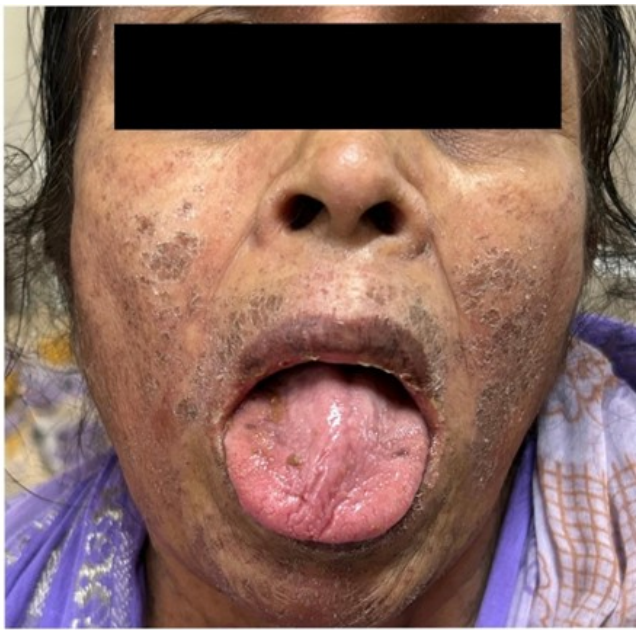
The patient was admitted to the Dermatology ward. Laboratory investigations revealed leukocytosis, neutrophilia, marked eosinophilia, impaired hepatic function and renal function, and elevated pancreatic enzymes. The patient's laboratory values upon admission are summarised in Table 1. Atypical lymphocytes were detected in peripheral blood smear. Blood cultures and tests for hepatitis B and C were negative. On the urine microscopic examination, occasional red blood cells were found. Mild proteinuria (1g/day) was detected on urinalysis. A stool examination ruled out other causes of eosinophilia such as parasitic infestations. Ultrasound of the abdomen revealed thickened cortical echogenicity and bilateral early renal pelvis dilatation. Echocardiography and chest radiography were insignificant.

The history of skin rash, facial puffiness, and drug exposure pointed towards the diagnosis of Allopurinol-induced DRESS syndrome. The possible offending drug, Allopurinol was stopped immediately. She was started on 40mg/day oral prednisolone and oral antihistamine along with local application of clotrimazole mouth paint and light liquid paraffin lotion. She was advised salt-restricted diet, adequate hydration and was prescribed 5mg oral sodium bicarbonate and 0.25mcg oral calcitriol.

During the follow-up, the patient's skin lesions began to regress along with gradual return of ALT, AST, amylase and lipase to normal limits over a period of 21 days. She was discharged and the dose of prednisolone was gradually tapered over 2 months. According to the WHO causality scale, the relationship between allopurinol and the adverse reaction was assessed and was determined to be 'Probable/Likely'.

Table 1. Laboratory investigations of the patient upon admission

Parameter	Patient's Value	Reference Range
Total leukocyte count	17,680	4000-10500 cells/cu. mm
Absolute neutrophil count	13437	2000-7000 cells/cu. mm
Absolute eosinophils count	1768	20-500 cells/cu. mm
ALT	169.5	5-31 IU/L
AST	112.7	5-31 IU/L
Amylase	236	28-100 U/L
Lipase	320	6-51 U/L
Urea	92	10-50 mg/dL
Creatinine	1.7	0.5-0.9 mg/dL
Uric acid	9.7	2.4-5.7 mg/dL
Total protein	5.7	6.4-8.3 gm/dL
Albumin	2.7	3.4-5.4 gm/dL
Albumin : Creatinine Ratio	119	<30 mg/gm



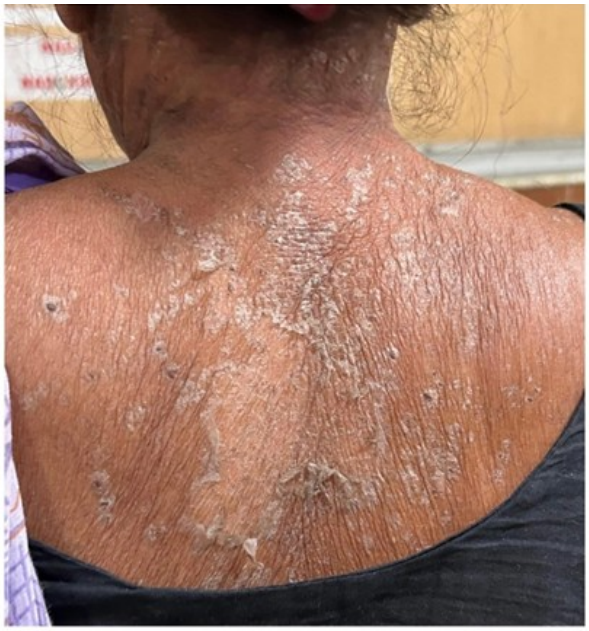


Fig. 2. Desquamation of skin over face, perioral region with tongue lesions, and back

DIFFERENTIAL DIAGNOSIS

- Toxic epidermal necrolysis
- Stevens-Johnson syndrome
- Hypereosinophilic syndrome
- Adult-onset Still's disease
- Kawasaki disease

DISCUSSION

DRESS syndrome is a T-cell mediated hypersensitivity (type IV) reaction, characterised by fever, generalised rash, facial oedema, lymphadenopathy, abnormal haematological profile and multiple organ involvement typically emerging 2-8 weeks after introducing the offending drug. Most cases of DRESS syndrome are precipitated by aromatic anticonvulsants, antibiotics, antipsychotics, and NSAIDs. High-risk drugs include allopurinol, carbamazepine, phenytoin, lamotrigine, vancomycin, sulfasalazine, amoxicillin, and dapsone[3]. The pathophysiology of DRESS syndrome is multifactorial, involving genetic predisposition, immune system dysregulation and latent viral reactivation. Genetic factors, particularly specific human leukocyte antigen alleles (HLA-B*58:01), contribute to an individual's susceptibility to this reaction. When a susceptible person is exposed to certain drugs, the drug or its reactive metabolites may interact with immune cells, particularly CD4+ and CD8+ T cells, triggering an abnormal immune response. This immune activation leads to the release of various cytokines and chemokines like interferon-gamma (IFN-γ), interleukin-4 (IL-4), IL-5, and IL-13, thereby promoting systemic inflammation and the recruitment of eosinophils and other immune cells. A distinguishing feature of DRESS is the frequent reactivation of latent herpesviruses, especially human herpesvirus 6 (HHV-6), which further amplifies the immune response contributing to tissue damage. These factors interplay to produce widespread inflammatory reactions affecting the skin, liver, kidneys, lungs and other organs[4]. The liver is the primary visceral organ involved in most cases of DRESS syndrome followed by the kidneys[10]. After absorption, allopurinol gets converted into its metabolite, oxypurinol which accumulates over a period of time potentially leading to the development of DRESS syndrome. Excess oxypurinol leads to tissue injury, inciting an immunological response and antibody production against tissue components with subsequent vasculitis[5]. Risk factors for allopurinol-induced DRESS syndrome include renal insufficiency, old age, higher allopurinol dose and concurrent thiazide diuretics usage[6]. In this case, impaired renal function may have played a role in the development of DRESS syndrome. Research indicates that oxypurinol elimination is closely linked to creatinine clearance, with minimal to no renal excretion of oxypurinol observed when creatinine clearance drops below 10 mL/min[7]. The diagnosis of DRESS syndrome is based on the RegiSCAR scoring system, which evaluates characteristic signs, symptoms, and laboratory results. Our case received a RegiSCAR score of 6 (fever, eosinophilia, atypical lymphocytosis, oedema and desquamation, skin rash extent >50%, liver, kidney and pancreas involvement, resolution in >15 days) making it a definitive case of DRESS syndrome[7]. The management of DRESS syndrome involves immediate discontinuation of the offending drug and administration of corticosteroids, antihistamines and emollients. Although systemic corticosteroids have not been evaluated in randomised clinical trials for the treatment of DRESS syndrome, they remain the most widely used supportive therapy. In case of life-endangering signs such as hemophagocytosis, liver failure, respiratory failure and encephalitis, intravenous immunoglobulin (IVIG) at a dose of 2 g/kg for five days along with systemic steroids are given[9]. In recent studies, other treatment options such as cyclosporine, mycophenolate, mepolizumab, and plasmapheresis were explored[10]. DRESS syndrome may lead to long-term sequelae such as vulnerability to functional changes in affected organs, end-organ failure, autoimmune diseases and possible multiple drug hypersensitivity, thus necessitating long-term monitoring of these patients[9].

CONCLUSION

This case highlights the development of DRESS syndrome following allopurinol ingestion in a 63-year-old female with renal insufficiency. Our case underscores the need for heightened awareness of drug toxicity reactions in geriatric patients receiving allopurinol. Allopurinol-induced DRESS syndrome carries a high risk of mortality, so caution is essential while prescribing this drug as well as careful consideration of the co-morbidities and associated risk factors. Surge in polypharmacy, prolonged latent period, and numerous suspect drugs delay DRESS recognition and prompt discontinuation of the culprit drug[4]. Enhanced education of patients and primary care physicians regarding allopurinol has the potential to mitigate the severity of adverse drug reactions, including rare reactions like DRESS syndrome, and improve clinical outcomes when such events arise.

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