A Case of Allopurinol-Induced Drug Reaction with Eosinophilia and Systemic Symptoms in a Patient With Polycystic Kidney Disease and Chronic Kidney Disease

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ABSTRACT

Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe drug hypersensitivity reaction.

Case Presentation: A 59-year-old male with a history of stage IV chronic kidney disease, polycystic kidney disease, hypertension, and hyperuricemia on allopurinol presented to the emergency department directly from an outpatient nephrology appointment with concern for severe DRESS syndrome with acute-on-chronic kidney failure, liver failure, and pancreatic involvement.

Discussion: The existing literature on the course of DRESS syndrome in patients with preexisting kidney dysfunction is limited.

Conclusions: We report a case of DRESS syndrome in a patient with chronic kidney disease who presented after initiating allopurinol for hyperuricemia. Care should be taken to quickly identify DRESS, stop the offending agent, and initiate systemic corticosteroids to prevent long-term morbidity and mortality. Furthermore, patient counseling should emphasize follow-up to identify and treat potential long-term sequelae, including thyroiditis and cardiac disease.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, drug-induced hypersensitivity reaction, with a mortality of approximately 10%.[1] DRESS typically manifests 2 to 8 weeks after initiating treatment with an offending drug, often an aromatic anticonvulsant, sulfonamide, or allopurinol. The existing literature on the course of DRESS syndrome in patients with preexisting kidney dysfunction is limited.

DRESS was first named in 1996.[2] However, the constellation of symptoms seen in DRESS initially was described as a "drug-induced pseudolymphoma" as early as 1959. The illness presents with a range of cutaneous, visceral organ, and immunological manifestations that were believed to constitute a drug-induced reaction.[1] Further investigations suggest that the aberrant immune response may be triggered by the presence of drug metabolites in the context of a genetic predisposition to altered drug metabolism, such as presence of the HLA-B58:01 allele. Patients with DRESS can present with an extensive and pruritic rash, fevers, lymphadenopathy, peripheral eosinophilia, and multiple organ involvement with onset of symptoms occurring 2 to 8 weeks after initiation of the offending drug. Acute visceral organ involvement can correlate with mortality. The 2 commonly involved organs include the liver and kidney, although isolated hepatic or renal involvement is possible as well. While preexisting kidney disease is not associated with increased mortality, patients with chronic kidney disease (CKD) who develop DRESS are at increased risk of progression into end stage renal disease.[3]

DRESS syndrome is one of several adverse drug reactions known as severe cutaneous adverse reactions. Of all cases of severe cutaneous adverse reactions, 5% are attributable to allopurinol.[4] We present a case of severe allopurinol-induced DRESS syndrome with widespread cutaneous, hepatic, pancreatic, and renal involvement. Given the rarity of DRESS syndrome, this case report aims to encourage the consideration of DRESS syndrome as the potential cause of cutaneous eruption with associated organ failure in patients taking associated pharmacologic agents. We also hope to contribute to the scant literature on DRESS syndrome outcomes in patients with CKD.

CASE PRESENTATION

A 59-year-old male with history of CKD IV due to polycystic

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kidney disease, hypertension, and hyperuricemia presented to a routine nephrology follow-up appointment where he was noted to have an extensive pruritic, erythematous papular rash on the trunk and extremities 2 months after starting allopurinol for hyperuricemia. The rash started on the left axilla and over 2 to 3 days spread to greater than 80% of the body surface area, sparing his palms, soles, face, and oral mucosa. This coincided with low-grade fevers and chills. He also took acetaminophen up to 4 grams daily for fevers. He was referred urgently to the dermatology clinic, where a punch biopsy of the rash was obtained, and he was started empirically on oral prednisone 100 mg daily for suspicion of DRESS syndrome versus acute generalized exanthematous pustulosis. He then was admitted directly to the hospital for close monitoring and treatment.

Upon admission, the patient was well-appearing and comfortable. He was tachycardic to 115, however was otherwise hemodynamically stable and afebrile. Lab results were notable for creatinine of 4.5 mg/dL elevated from his baseline of 2.5 mg/dL, absolute eosinophil 1850/uL, uric acid 7.7 mg/dL, aspartate transaminase (AST) 400 U/L, alanine transaminase (ALT) 1011 U/L, amylase 206 U/L, lipase 121 U/L, c-reactive protein 18.05 mg/dL, erythrocyte sedimentation rate 56 mm/hr, high-sensitivity troponin of 16 ng/L, HLA-B58:01 genotype negative. Additional labs are shown in Table 1. Punch biopsy of the rash showed spongiotic dermatitis with intraepidermal pustule and eosinophils. Chest x-ray, electrocardiogram, and transthoracic echocardiogram were unremarkable. He scored 7 on the RegiSCAR score,[5] a validated scoring system for evaluation of DRESS, indicating a definite diagnosis of DRESS (Table 2).

Dermatology was consulted for management of DRESS, and nephrology was consulted for management of acute kidney injury on CKD. Urine microscopy showed 5 to 10 white blood cells per high power field and occasional dark granular casts, suggestive of acute interstitial nephritis secondary to drug reaction. Per dermatology recommendations, the patient was continued on prednisone 100 mg daily with a gradual taper over 9 weeks and topical clobetasol as needed for pruritus. He also was started on pantoprazole for gastrointestinal prophylaxis and calcium supplement and vitamin D for prophylaxis against osteoporosis due to glucocorticoids.

On day 2 of admission, the patient exhibited decreased pruritus and improvement of the labs and remained hemodynamically stable. Repeat labs showed downtrending creatinine, AST, ALT, and amylase. On day 3, labs showed continued improvement in labs: creatinine 2.94 mg/dL (near the patient's baseline), AST 135 U/L, ALT 675 U/L, lipase 370 U/L, and absolute eosinophil 170/uL. Blood cultures obtained on admission were negative. He was discharged home with a plan for close outpatient follow-up with dermatology and nephrology with frequent trending of labs. He was counseled on strict adherence to the prednisone taper and return precautions to the emergency department.

Table 1. Patient's Laboratory Results Upon Admission and Rechecked at Time of Discharge

Lab Test	Day of Admission	Day 3 (Day of Discharge)	Reference Range
Blood			
White blood cell (10^3/µL)	10.5	11.9	3.9–11.2
Hemoglobin (g/dL)	12.9	10.9	13.7–17.5
Platelet (10^3/µL)	257	262	165–366
Absolute eosinophil (10^3/µL)	1.85	0.17	0.03–0.52
Eosinophil %	18	1	0–6
Peripheral smear, hematopathology review	Reactive lymphocytes	—	none
Blood urea nitrogen (mg/dL)	52	53	6–23
Sodium (mmol/L)	135	137	136–145
Potassium (mmol/L)	5.2	4.8	3.4–5.1
Chloride (mmol/L)	100	107	98–107
Bicarbonate (mmol/L)	21	18	22–29
Creatinine (mg/dL)	4.50	2.94	0.70–1.30
eGFR (mL/min/1.73 m^2)	16	26	≥60
Albumin (g/dL)	3.8	3.7	3.8–5.0
Alkaline phosphatase (units/L)	142	126	40–129
Aspartate transaminase (units /L)	400	135	<50
Alanine transaminase (units /L)	1,011	675	<42
Total bilirubin (mg/dL)	0.7	0.4	0.2–1.2
Lactic acid (mmol/L)	1.3	—	0.5–2.0
Phosphorous (mg/dL)	3.8	—	2.5–4.5
Magnesium (mg/dL)	2.2	—	1.6–2.6
Uric acid (mg/dL)	7.7	—	3.4–7.0
Lipase (units /L)	121	377	13–60
C-reactive protein (mg/dL)	18.05	—	<0.50
ESR (mm/hr)	56	—	0–25
Anti-nuclear antibody	Not detected	—	Not detected
Venous pH	7.34	—	7.32–7.42
Epstein-Barr virus	Not detected	—	Not detected
Cytomegalovirus	Not detected	—	Not detected
Hepatitis A antibody, IgM	Nonreactive	—	Nonreactive
Hepatitis B core antibody, IgM	Nonreactive	—	Nonreactive
Hepatitis B surface antigen	Nonreactive	—	Nonreactive
Hepatitis C Antibody	Nonreactive	—	Nonreactive
HLA-B58:01	Negative	—	Negative
Urine		-	
Urine bilirubin	Negative	Negative	Negative
Urine protein	Negative	Negative	Negative
Urine nitrite	Negative	Negative	Negative
Urine leukocyte esterase	Negative	Negative	Negative

Abbreviations: eGFR, estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate.

DISCUSSION

DRESS syndrome is a rare but serious adverse drug reaction. The epidemiology of DRESS is not fully understood, though estimates place the incidence at 1 in 1000 to 1 in 10000 drug exposures.[3] While the classic manifestation of the disease is cutaneous – most commonly presenting as a maculopapular rash that progresses to coalescing erythema – injury to visceral organs is common and may even present without cutaneous findings. The liver and kidneys are the most commonly involved visceral organs; other organs such as the lungs, heart, and thyroid also may be affected. Different HLA alleles confer a genetic predisposition to devel-

oping DRESS. For example, the HLA-B58:01 allele, which has the highest prevalence in the East Asian population,[6] has been shown to increase the risk of DRESS in patients who are started on allopurinol. A study of the Korean population found that among patients with CKD, significantly more patients with the HLA-B58:01 allele developed drug reactions compared to those who did not carry the HLA-B58:01 allele.[7] Furthermore, a study of the Han Chinese population reported a gene dosage effect of HLA-B58:01; ie, patients with homozygous HLA-B58:01 are at higher risk of DRESS than those with heterozygous HLA-B58:01.[8]

Kidney injury in DRESS warrants particular attention, not only because of the prevalence of kidney involvement, but also because preexisting renal impairment increases the risk for developing DRESS and its complications, including death. The aforementioned study of the Han Chinese population reported an additive effect of HLA-B58:01 positivity and preexisting CKD in the incidence of allopurinol-induced DRESS. Furthermore, the study found that the majority of deaths due to DRESS occurred in patients with preexisting severe renal impairment. While the reason for the increased risk for development and mortality from DRESS in patients with CKD is not fully understood, impaired clearance of the culprit medication, such as allopurinol, appears to play a role.[8]

Table 2. RegiSCAR Scoring System for Diagnosing DRESS

Items	Score			Comments	Patient Score
	-1	0	1		
Fever ≥ 38.5 °C	**N**/U	Yes			0
Enlarged lymph nodes		**N**/U	Y	>1 cm and ≥ 2 different areas	0
Eosinophilia ≥ 0.7 x 10^9/L or ≥ 0% if WBC < 4.0 x 10^9/L		N/U	**Y**	Score 2, when **≥ 1.5 x 10^9/L** or ≥ 20% if WBC < 4.0 x 10^9/L	2
Atypical lymphocytosis		N/U	**Y**		1
Skin rash, extent > 50% of BSA		N/U	**Y**		1
Rash suggesting DRESS	No	Unknown	**Y**	Rash suggesting DRESS: ≥ 2 symptoms: purpuric lesions (other than legs), infiltration, facial edema, psoriasiform desquamation	1
Skin biopsy suggesting DRESS	No	**Y**/U			0
Organ involvement		No	**Y**	Score 1 for each organ involvement, maximal score: 2	2
Rash resolution ≥ 15 days	N/**U**	Yes			-1
Excluding other causes		N/U	**Y**	Score 1 if 3 of the following tests were performed and all were negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture	1
					Total: 7

Abbreviations: ANA, anti-nuclear antibody; BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; N/U, no or unknown; WBC, white blood cells.

A score of < 2 indicates no case, 2–3 indicates possible case, 4–5 indicates probable case, > 5 indicates a definite case. The patient's RegiScar score at time of DRESS diagnosis is reflected in the far-right column (7; definite case of DRESS). The patient's score corresponding to each criterion is indicated in bold.

To date, there has been only 1 published case report of DRESS syndrome in a patient with polycystic kidney disease. In this report, a 51-year-old woman with a recent history of travel to rural Hunan and Szechuan, China, presented with DRESS that progressed to sepsis 3 weeks after starting allopurinol.

This case report highlights the importance of a broad differential that considers both infectious and noninfectious etiology, as well as knowledge of the medication history of a patient. Finally, this patient had the HLA-B58:01 haplotype, which has a known association with DRESS syndrome and may help guide clinical decision-making regarding allopurinol induction in patients with impaired kidney function.[9] There already exists American College of Rheumatology guidelines recommending HLA-B58:01 testing for patients of high-risk ethnicities prior to starting allopurinol.[10] However, these cases suggest that further research should investigate whether CKD also should be taken into consideration when deciding to test for HLA-B58:01 before starting allopurinol.

The increased risk of DRESS in patients with CKD poses challenges in the management of CKD and its complications. Allopurinol is one of the most prescribed medications for urate-lowering therapy and commonly is used to reduce the risk of urate-induced nephropathy. However, the benefits of initiating allopurinol must be weighed against the risk of drug hypersensitivity syndromes such as DRESS, which can lead to severe multiorgan damage, including to the kidneys. In a systematic review of 71 patients with DRESS syndrome with renal involvement, a majority had acute kidney injury.[3] This can be all the more serious in patients with baseline CKD, who are at higher risk of acute kidney injury requiring temporary or lifelong renal replacement therapy.[11]

Patients who have experienced DRESS are at risk of recurrence and, therefore, should be monitored with regular outpatient follow-up. Recurrence of DRESS can happen at any time following the initial event and can manifest in serious organ injury such as thyroiditis and myocarditis, as well as injuries to the liver and kidneys. The most common cause of recurrence is re-exposure to the offending drug. This can pose a serious challenge, as patients may continue to require treatment for the condition for which the culprit medication was intended to treat. Although the reasonable choice would be to switch to an alternative medication, even an alternative medication may trigger a recurrence of DRESS due to cross-reactivity with the initial medication. A number of such

cases have been reported involving allopurinol-induced DRESS, where recurrence of DRESS followed the initiation of febuxostat, another xanthine oxidase inhibitor that also is used to treat hyperuricemia.[12-16] Further research is needed to elucidate the cross reactivity of medications commonly associated with DRESS and reduce the risk of DRESS recurrence.

CONCLUSIONS

We report a case of DRESS syndrome in a patient with a history of chronic kidney disease resulting from polycystic kidney disease. The patient presented 6 weeks after initiating allopurinol for the treatment of hyperuricemia. Following the initiation of systemic corticosteroid treatment, his clinical picture improved rapidly and creatinine returned to baseline with no immediate concern for worsening of his CKD or progression to end-stage renal disease. While the incidence of DRESS is low, the mortality rate is approximately 10%. The utmost care should be taken to quickly identify DRESS, stop the precipitating agent, and initiate treatment with systemic corticosteroids to prevent long-term morbidity and mortality. Furthermore, patient counseling should emphasize the importance of long-term follow-up to identify and treat potential long-term sequelae, including thyroiditis and cardiac disease.

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