

Case Report Nephrology

Non-steroidal anti-inflammatory drug-induced DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome in a patient with multiple comorbidities

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an acute drug reaction involving numerous organs. It mostly occurs 2 to 8 weeks after the offending agent is administered and presents with fever, rash, lymphadenopathy, eosinophilia, and dysfunction of organs, especially the liver, kidneys, and lungs. Drug-specific T-cells seem to be responsible for the pathogenesis of this condition, and there is a genetic component, such as HLA-B58, 01, associated with allopurinol hypersensitivity, which influences this reaction. We describe a 54-year-old male patient known case of diabetes mellitus, hypertension, ischemic heart disease, and chronic kidney disease stage 5 who developed DRESS syndrome after using non-steroidal anti-inflammatory drugs (NSAIDs) for body aches and fever. The patient displayed typical signs, such as renal failure (requiring dialysis), a noticeable eosinophilia on complete blood count, and exfoliating dermatitis. The Regi severe cutaneous adverse reactions criteria were used to confirm the diagnosis. The present study highlights how NSAIDs can cause DRESS syndrome, especially in patients who have other comorbidities. It highlights the necessity of aggressive management, prompt diagnosis, and increased clinical awareness to avoid potentially significant consequences like multi-organ failure. This case is significant because it shows that DRESS syndrome may be reversible with early detection and treatment, highlighting the need for careful NSAIDs use and close patient monitoring in vulnerable people.

Keywords: Case report, Drug reaction, Drug reaction with eosinophilia and systemic symptoms, Eosinophilia, Non-steroidal anti-inflammatory drugs

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome was initially reported by Bocquet *et al.* as an episodic adverse drug reaction in 1996.^[1] Although originally described in patients treated with anticonvulsants in the 1930s, particularly phenytoin, this syndrome has now been linked to several drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) and allopurinol.^[1,2] It usually appears from two to eight weeks after the offending medication is first taken. Symptoms in clinical presentation include fever: 38–40°C, Rash: Maculopapular type, Lymphadenopathy: Peripheral lymph node enlargement, hematological disorders such as eosinophilia and atypical lymphocytes. Involvement of consolidating organs like liver, kidney and lungs is most frequent. Rare complications such as cholestasis have also been developed.^[3,4]

The etiology of DRESS syndrome remains incompletely understood. It is believed to be mediated by immunologic processes in conjunction with genetic differences in drug-detoxifying pathways.

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This clinical heterogeneity is regarded to be due to its genetic complexity.^[5] Among the patients, it has been reported that there are a number of different medications, although allopurinol is one of the best recognized. It is associated with high mortality; 10% in adults^[6] and 5.4% in children.^[7] Genetic factors contributing to DRESS syndrome have been established in multiple studies. Specifically, HLA-B58:01 is associated with allopurinol hypersensitivity, while HLA-B13:01 is associated with dapsone hypersensitivity.^[8,9] As a result, the so-called DRESS syndrome results from the activity of drug-specific T cells, thus constituting a drug-induced immune response. This condition often reactivates viruses, particularly human herpesviruses, probably due to the increase in T-reg cells.^[10]

While anticonvulsants and allopurinol are the most well-known culprits, NSAIDs have also been increasingly implicated in DRESS cases. A documented case of naproxen-induced DRESS syndrome demonstrated the diagnostic challenges associated with this condition, as the patient exhibited classical features including fever, rash, lymphadenopathy, and elevated liver enzymes. A scoring system, the Regi severe cutaneous adverse reactions (SCAR) criteria, was established to standardize the recognition of DRESS syndrome. The scale is a component of a European registry used to identify SCAR, such as harmful epidermal necrolysis, acute generalized exanthematous pustulosis, Stevens–Johnson syndrome, and DRESS.^[5] Although NSAID-induced DRESS remains relatively rare, its potential severity necessitates increased clinical vigilance, particularly in patients with multiple comorbidities or those on long-term NSAID therapy.^[11]

CASE REPORT

A 54-year-old male with type 2 diabetes mellitus (DM), hypertension, ischemic heart disease, and chronic kidney disease stage 5 (CKD-5) (with baseline creatinine level of 6 mg/dL) reported to nephrology clinic at Bahria International Hospital, Lahore with complaints of fever associated with sore throat for the past two days along with erythematous pruritic rash which was exfoliative in nature. Rash first appeared on his face and trunk, followed by the involvement of his extremities. The patient had been treated two weeks earlier at his local health center with intravenous diclofenac sodium (75 mg) and ketorolac tromethamine (30 mg) for fever and body aches. The patient additionally had no prior history of drug allergies.

During the examination, the patient was suffering from fever (100 F), and the rest of the vitals were normal. There was a diffuse, scaly, erythematous, exfoliative rash that was centripetal in distribution on the face, neck, and upper and lower limbs [Supplementary Figure 1]. The rash was sparing the lips, conjunctiva, oral mucosa with negative Nikolsky sign. (Nikolsky sign is positive when slight rubbing or

pressure on the skin causes the outer layer (epidermis) to shear off or detach from the lower layers.). He had bilateral cervical lymphadenopathy and mild facial edema along with non-blanching purpura on the lower limbs. On auscultation of the chest, there was decreased air entry at the bases, and the rest of the systemic examination was unremarkable. Initial blood work showed leukocytosis (white blood cell count $30.6 \times 10^3/\mu\text{L}$) with neutrophilia (79%), lymphopenia (3%), and marked eosinophilia (14%). Renal function panel showed acute kidney injury (AKI) on CKD, serum creatinine (11.13 mg/dL) and urea (147 mg/dL), and mild transaminitis present (aspartate aminotransferase 48 U/L and alanine aminotransferase 69 U/L). HBsAg, anti HCV, anti HIV were non reactive and ANA was also negative. Blood cultures and dengue serology were negative; complement levels (C3 and C4) were normal. Chest X-ray showed bilateral blunting of the costophrenic angles, and no consolidation was appreciated. Abdominal ultrasonography showed only mild hepatomegaly (161 mm), mild gallbladder wall edema, mildly enlarged spleen (88 mm), mild ascites, and grade 2 parenchymal disease of the kidneys. Echocardiography was normal.

On day 1, the patient's care team at the hospital treated him with a single shot of IV pheniramine maleate 25 mg and IV hydrocortisone 100 mg to counter what they initially thought to be a drug reaction. On day 2, he became febrile with worsening fevers and developed hypoxia with oxygen saturation of 88% at room air along with tachypnea and oliguria. Intravenous meropenem (500 mg 12-hourly, Renal adjusted dose) and oral linezolid (600 mg 12-hourly) commenced because of suspected sepsis. However, on day 3, leukocytosis worsened with persistent eosinophilia (40% of total leucocyte) and renal function further deteriorated (creatinine 12.2 mg/dL, urea 192 mg/dL) despite the above interventions. Hemodialysis was initiated because of progressive renal failure, acidosis, dyspnea, and oliguria, and a single session of hemodialysis was done with 2-L ultrafiltrate.

The patient showed a Regi SCAR DRESS score of 7, which led to the suspicion that he had DRESS syndrome after dermatology consultation. He was taken off antibiotics five days later. A diagnosis of DRESS syndrome was made, and the patient was commenced on intravenous methylprednisolone on day three (40 mg for five days), followed by an oral prednisolone tapering regimen starting at 60 mg for ten days. The patient had dramatic clinical improvement with urine output rising on day two of IV steroid therapy. On the eighth day of admission, serum creatinine decreased to 8.12 mg/dL, total leukocyte count dropped to $37.4 \times 10^3/\mu\text{L}$, and eosinophils up to 13%. The patient was discharged with an 8-day tapering steroid therapy. Biochemistry normalized within the first month, with complete resolution of symptoms and rash by week four.

Table 1: Outcomes of pertinent laboratory tests performed upon admission, throughout hospitalization, upon release, and during a one-month follow-up

Result	Hospital stays		Discharge	One-month follow-up	Normal range
	Day 1	Day 3			
Complete blood count					
White blood cells, $\times 10^3/\mu\text{L}$	30.6	62	37.4	9.3	4–11
Red blood cells, $\times 10^6/\mu\text{L}$	5.69	5.46	4.72	4.5	4.5–5.5
Platelets, $\times 10^3/\mu\text{L}$	221	265	252	217	150–450
Hemoglobin, g/dL	9.84	9.45	8.24	8.38	13.5–16.5
Hematocrit, %	34.9	33.3	28.8	30.2	40.0–50.0
Mean corpuscular volume, fL	61.3	61.1	61.1	66.3	80.0–95.0
Mean corpuscular hemoglobin, pg	17.3	17.3	17.4	18.4	27.0–32.0
Mean corpuscular hemoglobin concentration, g/dL	28.2	28.3	28.6	27.8	31.5–34.5
RDW, %	12.9	13.3	13.1	16.1	11.6–14
Neutrophil, %	79	51	65	94	40–80
Lymphocytes, %	3	6	18	3	20–40
Monocytes, %	4	3	4	2	2–10
Eosinophils, %	14	40	13	1	1–6
Comprehensive metabolic panel					
Urea, mg/dL	147	192	165	209	21–51
Creatinine, mg/dL	11.13	12.2	8.12	6.4	0.7–1.3
Total bilirubin, mg/dL	0.4			0.4	0.1–1.2
Alkaline phosphatase, U/L	337			174	50–116
Alanine aminotransferase, U/L	69			36	0–45
Aspartate aminotransferase, U/L	48			46	0–35
C-reactive protein, mg/L	81.9	78.2	33.6		0–5

This table includes the results of the CBC and comprehensive metabolic panel on Day 1 and Day 3 of hospitalization, as well as at discharge and 1-month follow-up. The results are compared to normal reference ranges, highlighting significant abnormalities in various parameters such as elevated white blood cell counts, anemia, and renal function impairment. The U/L shows the units per liter, and mg/dL shows milligrams per deciliter. RDW: Red cell distribution width.

DISCUSSION

Patients usually present with malaise, low-grade fever, and lymphadenopathy, and these symptoms are then followed by a rapidly progressing morbilliform rash that covers more than half of the body surface area. The morbilliform rash progresses to diffuse erythematous, exfoliative with scales, while facial swelling is another prominent feature. Laboratory tests on the DRESS syndrome have shown elevated leukocyte counts with eosinophils >700 cells/ microliter, with some atypical lymphocytes as illustrated in Table 1. The liver is the most common organ affected, and involvement occurs in 80–86% of patients, often presenting as hepatitis, jaundice, or multisymptomatic transaminitis. Kidney damage is seen in 20–30% of the patients, and the form is usually acute interstitial nephritis.

The histopathology of DRESS syndrome shows non-specific findings irrespective of some common patterns seen on skin

biopsies, such as interface dermatitis, spongiosis, damage to blood vessels, and superficial perivascular inflammation. These patterns suggest the disorder; however, the latter means that literature searches for DRESS will not yield any helpful diagnostic tips.

The European Regi SCAR group developed a scoring system that considers the illness course, clinical symptoms, skin and organ involvement, and more to diagnose DRESS syndrome. In this case, a score of Regi scar of 7 leads to definite DRESS syndrome [Table 2].

Stopping the offending drug is the most important measure for the treatment. In cases of extreme exfoliative dermatitis, patients may need an extra number of fluids, electrolytes, and drainage to help maintain nutrition. However, this patient had a dramatic clinical improvement with the commencement of IV corticosteroids, emphasizing heterogeneity of DRESS, and the necessity of Meropenem was started in this case as an empiric antibiotic in view of a possible septic condition.

Table 2: Score of Regi SCAR and its elements

Criteria	Presence	Score
Fever ($\geq 38.5^{\circ}\text{C}$)	Yes	0
Swollen lymph nodes (≥ 2 sites, ≥ 1 cm)	Yes	1
Unusual lymphocytes	No	0
Eosinophilia (>1500 cells or $>20\%$)	Yes	2
Skin rash		
Extent $>50\%$	Yes	1
At least two of: edema, infiltration, purpura, scaling	Yes	1
Biopsy suggesting DRESS syndrome	Unknown	0
Internal organ involved	One organ (kidney)	1
Resolution delay	>15 days	0
At least three biological investigations have been done and are negative to exclude an alternative diagnosis	Yes (blood cultures, anti-nuclear antibodies, and HAV/HBV/HCV serology).	1
7. (<2 no DRESS syndrome, <3 possible DRESS syndrome, $<4-5$ likely DRESS syndrome, ≥ 6 definite DRESS syndrome) is the total score. Regi SCAR is for Registry of severe cutaneous adverse reactions; DRESS stands for drug reaction with eosinophilia and systemic symptoms. SCAR: Severe cutaneous adverse reactions, HAV: Hepatitis A virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus.		

The patient was obviously immunocompromised (type 2 DM, CKD-5), and such patients are particularly vulnerable to severe infections. Therefore, broad-spectrum antibiotics should be started as soon as possible. It was a carbapenem and selected because of its effectiveness on both gram-negative and resistant microorganisms. This is an appropriate approach in establishing the diagnosis of empiric treatment when sepsis is the suspected clinical diagnosis, but no source can be identified, especially in immunocompromised patients.

Concerning the drug methylprednisolone, the use of intravenous methylprednisolone (40 mg) was a consensus with the dermatology department to initiate. We raised a strong concern about DRESS syndrome at this stage based on the patient's clinical manifestation and eosinophilia. The Regi SCAR score of 7 confirmed a high possibility of DRESS, and the dermatologist advised commencement of high doses of corticosteroids before the drug reaction became uncontrollable due to the widespread rash and suspicion of acute tubule-interstitial nephritis. The reason given for using these doses of corticosteroids in such conditions is to help manage the outcome of DRESS syndrome by controlling the overactivity of the immune system responsible for DRESS syndrome. A recent study, describing timely diagnosis and corticosteroids, commonly used, may not always provide the

best outcomes due to the potential for relapses and prolonged treatment courses. The study proposed the use of targeted therapies, such as cyclosporine, which has shown promise in reducing hospital stay and improving symptom resolution when compared to corticosteroids in DRESS patients. Furthermore, in our case of NSAIDs-induced DRESS syndrome, the renal involvement observed mirrors findings from a systematic review by Dagnon da Silva *et al.* (2023), where 96% of DRESS cases had AKI. Although NSAIDs are less commonly implicated, renal injury, including AKI, highlights the need for early diagnosis and intervention. As noted, nearly 30% of patients require renal replacement therapy, reinforcing the importance of vigilant monitoring to prevent relapses and long-term renal complications in DRESS syndrome.^[12]

Our case of NSAID-induced DRESS in a 54-year-old male with CKD contrasts with the naproxen-induced DRESS in a 40-year-old male with no comorbidities reported by Sasia *et al.*^[11] Their patient presented with fever, rash, eosinophilia, and liver involvement four weeks after naproxen use. Despite being initially treated as sepsis, the diagnosis was confirmed by Regi SCAR score,^[8] skin biopsy, and clinical correlation. The patient showed rapid recovery after systemic steroids and had no long-term complications. In contrast, our patient had earlier symptom onset (within two weeks), multi-organ involvement, and more severe complications, including respiratory compromise and dialysis-requiring AKI. While both cases demonstrated a strong response to systemic steroids, our case highlights the challenges of diagnosing DRESS in patients with comorbidities and overlapping symptoms. In addition, bacterial culture misinterpretation and delayed steroid initiation prolonged recovery. This comparison emphasizes the importance of early recognition and management of DRESS, particularly in vulnerable populations like those with CKD.^[11]

This case lacked histopathological confirmation through a skin biopsy, which may have provided more definitive insights into the cutaneous involvement and ruled out other differential diagnoses. Histopathological evaluation is often valuable in supporting a DRESS diagnosis, especially in atypical presentations or in the absence of classic symptoms.

Another limitation is the absence of genetic testing, particularly for known genetic markers such as HLA-B58:01, which has been associated with increased susceptibility to drug-induced hypersensitivity reactions, including allopurinol-related DRESS. Genetic screening could have strengthened the understanding of individual predisposition in this case.

Moreover, this study did not include long-term follow-up of the patient post-discharge. Given the potential for delayed complications, including autoimmune sequelae or relapse of organ dysfunction, long-term monitoring is essential to

assess the full impact of the condition and the effectiveness of the treatment provided. Finally, as this is a single case report, generalizability is limited.

CONCLUSION

Hence, this case highlights NSAIDs as a potential trigger for DRESS syndrome, particularly in patients with multiple comorbidities. Prompt recognition and initiation of corticosteroid therapy led to significant clinical improvement. The findings emphasize the importance of early intervention and careful monitoring of NSAID use in vulnerable individuals.

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