DRESS Syndrome: Improvement of Acute Kidney Injury and Rash with Corticosteroids

Dawnielle Endly, DO,* Jonathan Alterie, BS,** David Esguerra, DO,*** Richard A. Miller, DO****

*Co-lead Author, Dermatology Resident, Nova Southeastern University College of Osteopathic Medicine/Largo Medical Center, Largo, FL
**Co-lead Author, 4th-year Medical Student, Chicago College of Osteopathic Medicine, Chicago, IL
***Clinical Professor, Nova Southeastern University College of Osteopathic Medicine, Largo, FL
****Program Director, Dermatology Residency Program, Nova Southeastern University College of Osteopathic Medicine/Largo Medical Center, Largo, FL

Abstract

DRESS syndrome (drug rash with eosinophilia and systemic symptoms) is a rare and potentially life-threatening idiosyncratic drug reaction that may involve a number of visceral organs. This syndrome often mimics other serious systemic disease processes, making the diagnosis complicated and often delayed. Herein, we present a unique case of DRESS syndrome accompanied by acute interstitial nephritis that responded to oral prednisone during a hospital stay.

Introduction

DRESS syndrome is a drug reaction that usually manifests with fever, a pruritic macular and papular rash, hematologic abnormalities (leukocytosis, eosinophilia, and/or atypical lymphocytes), and internal organ involvement. This drug reaction is characterized by a delayed onset, typically occurring two to eight weeks after exposure to the inciting medication. Despite the existence of a scoring system known as RegiSCAR to aid in accurate and prompt diagnosis, the variability in the clinical course and dermatologic manifestations often results in delays.

Case Report

A 68-year-old female with history of type 2 diabetes mellitus, systolic heart failure with an ejection fraction (EF) of 25%, and Charcot-Marie-Tooth disease presented to the emergency department with progressive leg swelling and a diffuse, itchy rash of about two months' duration. The rash began on the left flank and face approximately four weeks after starting furosemide for fluid overload. No other new medications were initiated or modified in the prior six months. She denied fevers, joint pain, or facial swelling associated with the rash.

She was evaluated by an outside provider one week prior to hospitalization and was prescribed a mid-potency topical steroid cream to be applied twice a day to the most pruritic areas. A biopsy was obtained at that time, revealing sparse perivascular lymphohistiocytic infiltrate with frequent neutrophils and eosinophils in the superficial dermis. The patient reported minimal symptomatic relief, but the rash progressed and became generalized with total body involvement.

Upon admission, vital signs were all normal. Cutaneous examination revealed diffuse erythematous and violaceous macules and papules with fine white scale and several linear erosions with serosanguinous crusts (Figures 1-3). Both lower extremities had 2+ pitting edema up to the hips. No obvious facial edema, vesicles or bullae, or oral mucosal lesions were identified during hospitalization.

Initial laboratory results revealed various abnormalities. A complete blood count demonstrated an eosinophilia of 23% (normal 0-5%) and presence of atypical lymphocytes. A complete metabolic panel revealed many elevated components including: aspartate transaminase (AST) of 102 U/L (15-37 U/L), alanine transaminase (ALT) of 125 U/L (13-61 U/L), alkaline phosphatase of 263 U/L (45-117 U/L), blood urea nitrogen (BUN) of 65 mg/dL (7-18 mg/dL), and creatinine of 1.9 mg/dL (0.6-1.3 mg/dL) compared to her baseline creatinine of 1.0 mg/dL. Urinalysis was positive for leukocyte esterase, red blood cells 2-5/hpf (0-1/hpf), and white blood cells of 10-15/hpf (0-1/hpf). Urine eosinophils were also found to be positive. A urine culture eventually grew Escherichia coli, and she was treated for a urinary tract infection. Anti-nuclear antibody, blood cultures, a hepatitis panel, and rapid plasma regain (RPR) were all negative. An echocardiogram revealed a decrease in EF from 25% at baseline to 10% to 20% with severe diffuse hypokinesia and severe bialtrial enlargement. All clinical data was entered into the RegiSCAR group diagnosis chart for DRESS syndrome and revealed a total of 7 (see Table 1), confirming a diagnosis of DRESS syndrome.

Given multiple co-morbidities including uncontrolled diabetes, topical treatment with a high-potency topical steroid was initially favored. The possible causative medication, furosemide, had already been stopped prior to hospital admission. An echocardiogram revealed a decrease in ejection fraction to 15% to 20% with severe diffuse hypokinesia and severe bialtrial enlargement. Her renal function continued to decline throughout her hospitalization, and given the multitude of possible etiologies (preload from diuretics or heart failure exacerbation, possible interstitial nephritis secondary to DRESS syndrome), nephrology recommended a renal biopsy to aid in definitive diagnosis. On day four of her hospitalization, a renal biopsy was planned, but the patient became anxious and severely hypotensive while on the operating table. Unfortunately, the renal biopsy was not completed, and she required admission to the intensive care unit and vasopressors for several days while her renal function continued to decline.

The patient refused hemodialysis, but agreed to systemic steroids as treatment for possible interstitial nephritis secondary to DRESS syndrome. The patient initially received two intravenous doses of methylprednisolone 125 mg. She was then placed on an oral prednisone...
taper, and within a couple of days her BUN and creatinine began to decline and urine output began to increase. Additionally, there was substantial improvement in the patient's rash and pruritus. After a couple of days, the patient was taken off of vasopressors and determined to be stable for transfer back to the general medicine floor. She was ultimately discharged to a rehabilitation facility on a four-week prednisone taper.

Discussion

DRESS syndrome, or drug rash with eosinophilia and systemic symptoms, is an uncommon drug reaction that classically has a delayed onset within two to eight weeks after starting the causative medication.\(^1,3\) Incidence of this syndrome ranges from 1 in 1,000 to 1 in 10,000 drug exposures, with a mortality of 10%.\(^3,4\) Two studies noted a predilection for females, with a male-to-female ratio of 0.8:1.0.\(^2,5\)

DRESS syndrome was first attributed to aromatic anti-epileptic medications dating as far back as the 1920s, and it was thus referred to as anticonvulsant hypersensitivity syndrome. A case reported in 1950 describes a classic patient who presented with fever, an exfoliative rash, and jaundice while taking phenytoin.\(^6\) Another notable, early encounter that highlighted this often challenging diagnosis described a patient with lymphadenopathy, arthralgias, fever, and a pruritic rash mimicking malignant lymphoma while on carbamazepine.\(^7\)

While anticonvulsants remain the most frequently associated drug class, more and more different medications, such as sulfonamides, minocycline, allopurinol, ampicillin, and dapsone, are being deemed likely culprits. For this reason, the former nomenclature, anticonvulsant hypersensitivity syndrome, has fallen out of favor. In one study reviewing 201 potential cases of DRESS syndrome, aromatic anti-epileptic drugs were responsible for nearly 35% of cases.\(^2\) Also significant were the 12% of cases reported to have sulfonamides, particularly dapsone and sulfasalazine, as a possible cause.\(^2\) Despite sulfonamides being commonly suspect, our review of the literature revealed no reports of DRESS syndrome associated with furosemide, a non-antibiotic sulfonamide, prior to this case. Other, less frequently noted culprits are various antimicrobials, antivirals, antidepressants, anti-hypertensives, NSAIDs and biologic medications.\(^3,4\) While rarely reported to cause DRESS syndrome, minocycline is one antimicrobial worthy of highlighting, particularly for dermatologists. Of note, several studies report minocycline-induced DRESS syndrome occurs primarily in patients with darker skin types (Fitzpatrick V and VI).\(^5,10\) Maubec et al. proposes the higher melanin content in darker pigmented skin may form a melanin-minocycline complex resulting in accumulation of the causative drug.\(^10\)

It would be prudent for dermatologists to consider alternative therapies, perhaps doxycycline, in this specific patient population to help avoid DRESS syndrome and the potentially life-threatening sequelae that may result.

The most common skin finding reported in DRESS syndrome is a morbilliform or mixed macular and papular type of eruption. Exfoliative dermatitis following a diffuse erythroderma, facial swelling, mucosal involvement, and vesicles have also been reported in a number of studies.\(^1,2,4\) Cacoub et al. found 97% of those suffering from DRESS syndrome in their study actually had a rash.\(^3\) More specifically, 60% exhibited a macular and papular rash, 54% had a generalized erythematous rash, and 39% had facial edema.

In addition to the cutaneous manifestations, internal organ involvement is another variable entity in DRESS syndrome. According to Husain et al., the most commonly affected visceral organ is the liver.\(^4\) They found nearly 70% of patients with DRESS syndrome to have abnormal liver function tests. The renal system is less commonly involved. Effects on the kidney can lead to hematuria, proteinuria and elevated BUN and creatinine. The appearance of eosinophils in the

discussion

DRESS syndrome, or drug rash with eosinophilia and systemic symptoms, is an uncommon drug reaction that classically has a delayed onset within two to eight weeks after starting the causative medication.\(^1,3\) Incidence of this syndrome ranges from 1 in 1,000 to 1 in 10,000 drug exposures, with a mortality of 10%.\(^3,4\) Two studies noted a predilection for females, with a male-to-female ratio of 0.8:1.0.\(^2,5\)

DRESS syndrome was first attributed to aromatic anti-epileptic medications dating as far back as the 1920s, and it was thus referred to as anticonvulsant hypersensitivity syndrome. A case reported in 1950 describes a classic patient who presented with fever, an exfoliative rash, and jaundice while taking phenytoin.\(^6\) Another notable, early encounter that highlighted this often challenging diagnosis described a patient with lymphadenopathy, arthralgias, fever, and a pruritic rash mimicking malignant lymphoma while on carbamazepine.\(^7\)

While anticonvulsants remain the most frequently associated drug class, more and more different medications, such as sulfonamides, minocycline, allopurinol, ampicillin, and dapsone, are being deemed likely culprits. For this reason, the former nomenclature, anticonvulsant hypersensitivity syndrome, has fallen out of favor. In one study reviewing 201 potential cases of DRESS syndrome, aromatic anti-epileptic drugs were responsible for nearly 35% of cases.\(^2\) Also significant were the 12% of cases reported to have sulfonamides, particularly dapsone and sulfasalazine, as a possible cause.\(^2\) Despite sulfonamides being commonly suspect, our review of the literature revealed no reports of DRESS syndrome associated with furosemide, a non-antibiotic sulfonamide, prior to this case. Other, less frequently noted culprits are various antimicrobials, antivirals, antidepressants, anti-hypertensives, NSAIDs and biologic medications.\(^3,4\) While rarely reported to cause DRESS syndrome, minocycline is one antimicrobial worthy of highlighting, particularly for dermatologists. Of note, several studies report minocycline-induced DRESS syndrome occurs primarily in patients with darker skin types (Fitzpatrick V and VI).\(^5,10\) Maubec et al. proposes the higher melanin content in darker pigmented skin may form a melanin-minocycline complex resulting in accumulation of the causative drug.\(^10\)

It would be prudent for dermatologists to consider alternative therapies, perhaps doxycycline, in this specific patient population to help avoid DRESS syndrome and the potentially life-threatening sequelae that may result.

The most common skin finding reported in DRESS syndrome is a morbilliform or mixed macular and papular type of eruption. Exfoliative dermatitis following a diffuse erythroderma, facial swelling, mucosal involvement, and vesicles have also been reported in a number of studies.\(^1,2,4\) Cacoub et al. found 97% of those suffering from DRESS syndrome in their study actually had a rash.\(^3\) More specifically, 60% exhibited a macular and papular rash, 54% had a generalized erythematous rash, and 39% had facial edema.

In addition to the cutaneous manifestations, internal organ involvement is another variable entity in DRESS syndrome. According to Husain et al., the most commonly affected visceral organ is the liver.\(^4\) They found nearly 70% of patients with DRESS syndrome to have abnormal liver function tests. The renal system is less commonly involved. Effects on the kidney can lead to hematuria, proteinuria and elevated BUN and creatinine. The appearance of eosinophils in the

Table 1. RegiSCAR score for DRESS syndrome\(^11\)

<table>
<thead>
<tr>
<th>Features</th>
<th>No</th>
<th>Yes</th>
<th>Unknown</th>
<th>Current Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (≥ 38.5°C)</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>Enlarged lymph nodes (≥ 2 sites, ≥ 1 cm)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>700–1,499 or 10%–19.9%</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,500 or ≥ 20%</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent &gt; 50%</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>At least 2 of: edema, infiltration, purpura, scaling</td>
<td>-1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Biopsy suggesting DRESS</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Internal organ involvement</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2 or more</td>
<td></td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Resolution in more than 15 days</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Rule out ≥ 3 other potential causes (ANA, blood cultures, hepatitis panel, RPR, chlamydia, etc.)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Final Score</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>
the decision to begin systemic corticosteroids is dependent upon the overall clinical picture and whether there are signs of visceral involvement. In the absence of internal organ involvement or when transaminase levels do not exceed five times normal, patients may be treated conservatively with topical corticosteroids. In addition, treatment may include H1-antihistamines and emollients for symptomatic relief if pruritus is present. In the presence of visceral involvement and/or elevated transaminase levels greater than five times normal, 1 mg/kg/day of prednisone with a taper regimen over three to six months is warranted. In the case that no improvement is noted with oral prednisone, a three-day course of 30 mg/kg of methylprednisolone intravenously may be administered as pulse therapy. 

Even with cessation of the causative medication, mortality is reported to be around 10%. However, just as there is variability in DRESS syndrome’s clinical presentation, the mortality varies according to the patient’s comorbidities, presence or absence of visceral involvement, and amount of time from disease onset to diagnosis and treatment.

**Conclusion**

As evident in this particular case, DRESS syndrome is a challenging diagnosis of exclusion that has the potential to progress to a life-threatening illness warranting the use of systemic corticosteroids. The clinical picture is often broad and non-specific, requiring a detailed history. It is important to note the temporal evolution of signs and symptoms, use sound physical exam skills, and closely interpret laboratory values to make the diagnosis of DRESS syndrome. The culprit medication should be discontinued as soon as possible, and the decision to treat with topical or systemic corticosteroids must be based on clinical severity.

**References**


**Correspondence:** Dawnielle Endly, DO; Dawnielleendly@hotmail.com

---

**Table 2. Visceral organs most commonly affected by DRESS**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>75%</td>
</tr>
<tr>
<td>Kidney</td>
<td>37%</td>
</tr>
<tr>
<td>Lung</td>
<td>32%</td>
</tr>
<tr>
<td>Spleen</td>
<td>15%</td>
</tr>
<tr>
<td>Heart/Musculoskeletal</td>
<td>13%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Table 3. RegiSCAR inclusion criteria for DRESS syndrome**

- **Hospitalization+**
- **Reaction suspected to be drug-related+**
- **Acute skin rash+**
- **Fever above 38°C**
- **Enlarged lymph nodes in at least two sites**
- **Involvement of at least one internal organ+**
- **Lymphocytes above or below the laboratory limits**
- **Eosinophilia+**
- **Thrombocytopenia**

*At least 3 required for diagnosis

+Inclusion criteria in current case

*See Table 2 for a list of the most commonly affected visceral organs in DRESS syndrome.*

Due to the variability in presentation, relatively late onset, and long duration even after stopping the causative drug, DRESS syndrome is often a complex, delayed diagnosis. It is important that clinicians first exclude other clinically similar conditions such as lymphoproliferative diseases and autoimmune or infectious diseases. When considering DRESS syndrome, the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria aid in solidifying a diagnosis when confronted with these clinically challenging cases (Table 1). Additionally, RegiSCAR requires three or more of the following major criteria for a solid diagnosis of DRESS syndrome: an acute rash, fever above 38°C, lymphadenopathy of at least two sites, involvement of at least one internal organ, platelets below normal laboratory limits, lymphocytes above or below the laboratory limits and/or increased eosinophil counts (Table 3). Additional criteria to consider, though not necessarily required for a diagnosis of DRESS syndrome, include hospitalization and/or a suspected drug-related etiology.

Once DRESS syndrome is suspected, discontinuation of the offending agent is the first step in treatment. According to Husain et al.,