# DRESS Syndrome Without Eosinophilia Presented with Extensive Skin Rash and Acute Respiratory Failure

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**Keywords:** DRESS syndrome, Sulfasalazine, Hydroxychloroquine, Herpes viruses' reactivation

**Key Clinical Message**

This case demonstrated the complex pathophysiology of DRESS syndrome presenting with latent human herpesvirus infection reactivation due to exposure to sulfasalazine and/or hydroxychloroquine. Patients who do not initially fulfill the diagnostic criteria on admission may evolve and eventually fulfill the criteria.

Steroid dose tapering is required to prevent flaring.

**Introduction**

Drug reaction with eosinophilia and systemic symptoms (DRESS) is also known as drug-induced hypersensitivity (DiSH) or drug-induced delayed multi-organ hypersensitivity syndrome. It is one of the severe cutaneous adverse reactions to drugs (SCAR) syndrome, characterized by cutaneous features of variable morphology and systemic organ involvement [1,2]. Certain genetic predispositions and drug-virus interactions are hypothesized to be the underlying pathogenesis of DRESS [2,3]. Herein, we report a case of a young female who developed DRESS with acute respiratory failure due to sulfasalazine/hydroxychloroquine with reactive Ebstein-Barr virus and human herpes virus-6.

**Case Description**

A 23-year-old female patient who was commenced on sulfasalazine and hydroxychloroquine five weeks ago for a newly diagnosed seronegative rheumatoid arthritis presented for evaluation of a 10-day history of progressive skin rash, which initially started on her trunk and spread peripherally to her extremities, neck, and face. She stopped her medications since the onset of the rash; however, her facial swelling and redness

had increased over the past few days before the presentation. She also reported subjective fever, chills, dry cough, and joint pains in the lower extremities.

On examination, she was feverish with a temperature of 103 °F, tachycardic with a heart rate of 110 beats per minute, a blood pressure of 100/60 mmHg, tachypneic with a respiratory rate of 25 per minute, and an oxygen saturation of 90% at room air. Cervical lymphadenopathy and hepatosplenomegaly were noted. Skin examination revealed widespread erythematous morbilliform eruptions distributed on the trunk and extremities, including palms and soles, covering approximately 80 % of the total body surface area (TBSA) with follicular accentuation on the lower extremities. Confluent erythema of the face with facial edema with multiple discrete perifollicular pustules were observed along the frontal hairline and throughout the scalp. No oral or vaginal mucosal involvement or desquamation was observed. (Figure 1 Panel A-C). The lung examination was unremarkable, but a stridor was noted, for which she was intubated for airway protection.

**Methods**

Initial laboratory workup showed leukocytosis with a white blood cell count (WBCs) of 24.8 K/uL (normal range:4.23-9.07 K/uL) with no eosinophilia or atypical lymphocytes, transaminitis with mildly elevated alanine transferase (ALT) at 55 IU/L (normal range: 5-41 IU/L), C-reactive protein was high at 2.7 mg/dL (normal range: 0-0.5 mg/dL) otherwise unremarkable including urine analysis, respiratory viral panel, cultures, renal and thyroid functions. An autoimmune panel including antinuclear (ANA), anti-double-stranded DNA (dsDNA), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (CCP) were negative. Screening for hepatitis A, B, and C viruses was reactive only for hepatitis A virus IgG. Ebstein-Barr virus (EBV) nuclear Ag IgG, EBV viral capsid antigen (VCA) IgG, and IgM were positive, while human herpesvirus-6 (HHV-6) PCR was high at 1,537 copies/mL, indicating late primary infection or possible reactivation. Differential diagnosis included drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome versus acute generalized exanthematous pustulosis (AGEP). A skin biopsy of pustule from her frontal hairline was performed, demonstrating epidermal spongiotic psoriasiform dermatitis with yeast folliculitis and a dermal infiltrate of lymphocytes, some of which exhibit moderate cytologic atypia (reactive lymphocytes), consistent with DRESS over AGEP, with coexisting yeast folliculitis. (Figure 2 Panel A-B).

Given fever, leukocytosis, transaminitis, the temporal relationship between drug exposure and symptoms onset, positive EBV serology and HHV-6 PCR, and progression of the rash despite cessation of offending drugs, the diagnosis favors DRESS secondary to sulfasalazine and/or hydroxychloroquine with possible EBV and HHV-6 reactivation rather than primary infection.

**Results**

She was started on methylprednisolone 40 mg every 12 hours, diphenhydramine for itchiness as needed, 2.5% topical hydrocortisone ointment twice daily on facial rashes, 0.1% triamcinolone topical twice daily for rashes elsewhere other than face and topical ketoconazole shampoo for yeast folliculitis. She was successfully extubated within 48 hours with gradual resolution of her facial edema and rash. She was discharged on oral prednisone 40 mg daily with planned slow tapper as an outpatient.

**Discussion**

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DiHS) is a severe adverse idiosyncratic type IV hypersensitivity drug reaction characterized by an extensive skin rash and systemic organ involvement, lymphadenopathy, eosinophilia, and atypical lymphocytosis [1,2]. The combination of certain genetic predispositions and drug-virus interactions has been hypothesized to be the underlying pathogenesis of DRESS [2,3]. Certain Human leukocyte antigens (HLA) alleles have been associated with an increased risk of developing drug-specific DRESS in certain population groups [3]. Common drugs causing DRESS include aromatic antiepileptics, allopurinol, and sulfonamide drugs [2-4]. Two main theories describing the pathophysiology of DRESS involve drug-specific T-cell reactions and viral reactivation [1,2]. Firstly, an immune response against the drug reactivates viral infection. Secondly, concomitant immune response to viral reactivation is responsible for clinical manifestations of DRESS syndrome [1,4,5]. Human

herpesvirus including cytomegalovirus (CMV), Ebstein-Barr virus (EBV), human herpes virus-6 (HHV-6), and human herpes virus-7 (HHV-7) is often associated with DRESS syndrome [2,3]. Quantitative PCR of viral DNA is the method of choice to determine active viral infection, primary or reactivation [6]. HHV-6 and EBV appear to be detected earlier in the course of the disease, followed by HHV-7 and CMV. This sequential viral reactivation suggests that it is related to the clinical phase of DRESS [2].

Clinical manifestations usually appear between 2 to 8 weeks after the introduction of the triggering drug [1,2]. With re-exposure, the time to onset is shorter with a more severe presentation [2,3]. The cutaneous eruptions usually begin with morbilliform eruption and later become edematous with follicular attenuation and can, less commonly, present with urticaria, erythroderma, vesicles, bullae, and pustules. Facial and neck edema is a hallmark, while mucosal involvement is rare and mild [2,3]. The systemic manifestations that commonly present and are part of the diagnostic criteria comprise fever, hematological abnormalities (leukocytosis, eosinophilia, and/or positive atypical lymphocytes), lymphadenopathy, and elevated liver function tests. Other possible internal organ involvements include kidneys (interstitial nephritis), lungs (pneumonitis), pancreas (pancreatitis), thyroid (thyroiditis), and heart (myocarditis, pericarditis). These organ involvements are the major causes of morbidity and mortality, which range from 2-10% [2-4] The most severe and life-threatening complication is fulminant liver failure [3,4]. Because of the systemic involvement features, DRESS is commonly mistaken for sepsis; a careful investigation must be undertaken to exclude sepsis as a cause of the patient's clinical manifestations. Other severe cutaneous adverse reactions (SCAR) syndrome like Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) or AGEP should also be considered in the differential diagnosis. However, the onset of eruption—shorter in SJS/TEN and AGEP– can help distinguish DRESS from the rest [2].

Diagnostic criteria commonly utilized are the RegiSCAR criteria for hospitalized patients with DRESS syndrome and a Japanese group's criteria for diagnosis of DRESS/DIHS; the main difference is the inclusion of HHV-6 reactivation in the latter [3,4]. Patients who do not initially fulfill the diagnostic criteria on admission may evolve and eventually fulfill the criteria [2]. However, the diagnostic gold standard remains drug re-challenge, which is not practical due to life-threatening consequences [2,4]. An alternative is a patch test of the offending drug, which is positive in approximately 60% of the cases [7]. Previous data showed that around 10% of patients diagnosed with DRESS syndrome had normal eosinophilic count, and 30-50% had no lymphadenopathies, making the diagnosis more challenging. Proper clinical history and temporal relation with drug exposure can increase the accuracy of diagnosis and improve the overall prognosis [8].

Regardless of the proposed pathogenic mechanisms of DRESS syndrome, there is no difference in management [1]. Early cessation of the offending drug and all unnecessary drugs is essential for improved prognosis and shorter duration [1,2]. Supportive therapies such as intravenous fluids and antipyretics may be required to maintain hemodynamics [2,3]. Corticosteroids are the first line of treatment, either topical to relieve itchiness or systemic [2-4]. However, most of the cases require systemic corticosteroid therapy. If oral therapy fails or intravenous therapy is required, pulse therapy with methylprednisolone is indicated [2]. Steroid tapering dose varies from 1 to 3 months based on the clinical course [2,3,5]. In steroid-refractory cases, immunosuppressive therapies such as ciclosporin, cyclophosphamide, rituximab, or intravenous immunoglobulin (IVIG) can be used [1,2]. Cutaneous and systemic involvement can persist for several weeks to months after drug withdrawal or following systemic corticosteroid tapering [2,3]. Follow-up is required as patients can develop autoimmune phenomena or thyroid dysfunction following DRESS syndrome.

## Conclusion

The severity of cutaneous manifestations of DRESS syndrome varies, but systemic involvement is the main cause of morbidity and mortality and requires close monitoring during hospitalization. The disease course can continue to progress even when the triggering drug is discontinued. Some patients may not respond to oral corticosteroids and require high-dose intravenous corticosteroid therapy, with disease flares that can also occur during the steroid dose tapering. Future administration of the drug-induced DRESS is contraindicated due to the potential risk of recurrence and complications.

## AUTHOR CONTRIBUTIONS

Nattanicha Chaisrimaneepan: writing – original draft; writing – review and editing.

Corley Pruneda: resources

Marwan Elmassry: Validation

Mahmoud Abdelnabi: Conceptualization, supervision

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## CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

## CONSENT

Verbal and written consent was obtained from the patient to publish this case.

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