



# DRESS Syndrome in a Teenage Male Associated With HHV-6 Reactivation While On Prolonged TMP-SMX Use: A Case Report and Review of the Literature

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## Abstract

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare and potentially life-threatening systemic drug reaction with skin involvement. We present the unusual case of DRESS in a 16-year-old male that was treated with TMP-SMX for acne and was initially misdiagnosed with Steven Johnson Syndrome. Our case serves as an example to healthcare providers treating adverse drug reactions to have a high clinical suspicion for DRESS as delay in diagnosis and treatment can result in disseminated disease and higher patient mortality risk.

**Keywords:** DRESS syndrome; Eosinophilia; Adverse drug reaction; HHV-6 reactivation; Bactrim adverse reaction

## Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare and potentially life-threatening systemic drug reaction with skin involvement. The estimated incidence is from 1/1,000 to 1/10,000 after drug exposure [1-4]. Common drugs associated with DRESS syndrome include aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine, lamotrigine) and antibiotics (TMP-SMX, minocycline, vancomycin), along with many other drugs that are continuously being added to the list. Symptoms are usually delayed 2-6 weeks after drug introduction. The classic signs include fever, rash, internal organ involvement and haematological abnormalities. Although DRESS is more prevalent in adults than children, it is important to distinguish this syndrome from other conditions as the mortality rate is 10%. It can be a challenge to arrive at the correct diagnosis since not all signs and symptoms may be evident at presentation. In addition, therapy for DRESS is distinct

from other T-cell derived drug reactions [5]. General knowledge of this syndrome would be beneficial to have when a cutaneous adverse drug reaction is suspected. In this report, we describe a case of DRESS syndrome secondary to prolonged antibiotic use of TMP-SMX in a teenage male. Our goal is to emphasize the clinical presentation of DRESS syndrome, highlight certain unique characteristics of this case, and review the diagnostic criteria and management of DRESS syndrome.

## Case Report

A 16-year-old male with a history of mild intermittent asthma and under a 5-week course of TMP-SMX for acne treatment presented with a rash. One week prior to admission, he experienced headache, generalized itchiness, and emesis which prompted him to discontinue TMP-SMX. Three days prior to admission, he developed an erythematous rash on his chest and fever. Two days prior to admission, he went to an urgent care where he was given amoxicillin and a steroid injection. The

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following day, the rash started to spread covering about 90% of his body surface area. He was seen at another facility and was transferred to our hospital for suspected Steven Johnson Syndrome (SJS).

Initial labs included WBC  $18.4 \times 10^9$  cells/L with segments of 68%, bands 8 %, lymphocytes 6%, monocytes 2%, eosinophils 6%, atypical lymphocytes 7%, metamyelocytes 2%. Absolute eosinophil count (AEC) was 1100. Total bilirubin 5.1, AST 250, ALT 820 and GGT 265. Physical exam was significant for diffuse cutaneous lesions in the form of dusky non-blanching erythematous macules with atypical target-like lesions without desquamation or blisters. He had bilateral scleral icterus and some oropharyngeal mucosal involvement, but no conjunctival association. He was started on methylprednisone for cholestatic hepatitis and concern for SJS.

An abnormal ultrasound showed hepatomegaly of 19 cm. various serological tests were obtained in an effort to find the cause of the hepatitis. This included viral panels for cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human immunodeficiency virus, which were negative. Respiratory viral panel, autoimmune hepatitis panel and viral hepatitis panel were negative. The mycoplasma pneumonia antibody was 686 U/ML



**Figure 1:** Patient skin presentation in both upper and lower extremities at time of hospitalization

with mycoplasma pneumonia IgM 1578 U/ML. However, mycoplasma pneumonia PCR was negative. On hospital day 6, WBC was  $20.4 \times 10^9$  cells/L with eosinophils 16% and atypical lymphocytes 14%. Total bilirubin 10, direct bilirubin 7.7, AST 617 and ALT 2333. Due to an AEC of 3200 and atypical lymphocytes, there was a high suspicion for DRESS syndrome. Hence, a skin biopsy of the right calf was performed,

which demonstrated interface dermatitis with superficial perivascular lymphoid histiocytic infiltrate with eosinophils and extravasated erythrocytes. In addition, Human Herpes Virus 6 (HHV-6) Qualitative PCR was collected, which later returned positive. After hospital discharge, there was close follow up and management of an oral steroid taper by the allergy/immunology and gastroenterology departments (Figure 1).

## Discussion

### Diagnostic criteria

There are no standard diagnostic criteria for DRESS syndrome. However, there are 3 different sets of criteria that are commonly used (Table 1). Bocquet et al proposed the original criteria which includes: (1) drug eruption; (2) hematologic abnormalities (i.e., eosinophilia  $> 1.5 \times 10^9$  cells/L and the presence of atypical lymphocytes); and (3) systemic manifestations (i.e., adenopathy with lymph nodes  $> 2$  cm; hepatitis with transaminase levels twice the normal values, interstitial nephritis; pneumonitis, and carditis) [6]. In retrospect, our patient met diagnosis of DRESS upon admission under the Bocquet criteria.

In 2007, The European Registry of Severe Cutaneous Adverse Reactions to Drug and Collection of Biological Samples (RegiSCAR) developed criteria which contain 7 characteristics of which the first three have to be met in addition to 3 out of 4 subsequent listed features [7]. In 2006, criteria proposed by the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J- SCAR) group also comprise 7 standards which are all required for diagnosis of drug induced hypersensitivity syndrome (DIHS) [8]. Their criteria highlight the role of HHV-6 reactivation in DRESS syndrome (Table 1).

A retrospective study comparing the criteria concluded that Bocquet's criteria are simple to use and appropriate to diagnose [9,10]. Furthermore, it was suggested to use in conjunction the RegiSCAR criteria when suspecting DRESS. Interestingly, our patient satisfied 6 out of 7 RegiSCAR criteria, 6 of 7 for J-SCAR and all for Bocquet's. The drug of suspicion was of the sulfonamide class, which is a known trigger. The most common organ involved was the liver. He was also positive for HHV-6, which is linked to DRESS and noted by J-SCAR criteria [6]. The most common skin biopsy findings were perivascular lymphocytic infiltrate in the papillary dermis with extravasated erythrocytes, eosinophils and dermal edema, which our patient also demonstrated [3].

### Pathogenesis

DRESS is believed to be an erroneous drug

hypersensitivity reaction occurring in 2.18 out of 100,000 patients [11]. These patients are believed to have very reactive type II innate lymphoid cells that produce high levels of ST2, which in turn initiate the classical DRESS skin eruptions [12]. It has also been suggested that reactive drug metabolites may mediate immune response and induce reactivation or propagation of HHV-6 [9]. The association between HHV-6 active infection and cutaneous drug adverse reactions seems to be specific to DRESS. A prospective study showed that DRESS is a result of cutaneous and systemic manifestation of an immune

response, mainly mediated by CD8+ T lymphocytes directed against herpes virus antigens, which include HHV-6, HHV-7, EBV and CMV [10]. This is supported by the clinical features of DRESS which are consistent with viral infection. It has been proposed that testing for herpes virus activation be done for suspected cases as an aid in diagnosis. The main feature of HHV-6 is the virus capacity to infect T-cells. There have also been indications that specific human leukocyte antigen (HLA) variants may also put certain people at increased risk [1].

Bocquet	RegiSCAR	J- SCAR
Skin Eruption	Skin eruption	Maculopapular rash developing > 3 weeks after starting offending drug
Blood eosinophilia (>1.5×10 <sup>3</sup> /μL) or the presence of atypical lymphocytes	Reaction suspected to be drug related	Prolonged clinical symptoms after discontinuation of causative drug
Internal organ involvement, including lymphadenopathies (>2 cm in diameter), hepatitis (liver transaminases values > twice the upper normal limit), interstitial nephritis, and interstitial pneumonia or carditis	Hospitalization	Fever (>38 C)
	Fever (>38 C)	Liver abnormalities (ALT > 100 U/L) or other internal organ involvement
	Lymphadenopathy involving 2 sites	Leukocytosis, Atypical lymphocytosis and Eosinophilia
	Involvement of at least 1 internal organ	Lymphadenopathy
	Hematologic abnormalities (abnormal lymphocyte count, eosinophilia or thrombocytopenia)	HHV-6 reactivation

Table 1: The most commonly used diagnostic criteria for DRESS

### Management

The first step in treatment is to stop the suspected offending agent. It is important to take a detailed history as the patient may be taking different drugs. Thus, having a timeline of when signs

and symptoms began is helpful as to distinguish SJS, TEN, AGEP and erythroderma from that of DRESS, considering each have a typical onset time of the skin eruption. In addition, knowing the other characteristic findings for each is also important (Table 2).

	AGEP	Erythroderma	SJS	TEN
Time of onset	48 hours	1-3 weeks	Days to 3 weeks	Days to 3 weeks
Skin manifestations	Edema, pustules, tense bullae	Erythema and scaling of >90% of BSA	Dusky erythema, atypical target lesions (<10% of BSA) and mucocutaneous erosions	Dusky erythema, atypical target lesions, erosions and bullae (>30% of BSA), mucosal involvement
Systemic involvement	Possible	Possible	Fever, malaise, tubular nephritis	Fever, malaise, tubular nephritis, eye involvement, tracheobronchial necrosis

Table 2: Comparison of various severe cutaneous adverse reactions

Therapy with systemic corticosteroids is the most widely accepted treatment [5]. Although no controlled studies have been published to date, improvement of symptoms and laboratory values are seen days after initiation of steroids. It is important to note that rash and hepatitis may still persist for weeks. Once outpatient status occurs, it has been recommended to undergo a prolonged steroid taper and appropriate lab monitoring.

## Conclusion

Our case was a diagnostic challenge as it originally presented without recognizing the peripheral eosinophilia (consisting of an AEC of 1100) and with a morbilliform rash that had irregular borders and mimicked the outer edge of a target lesion, leading to an initial diagnosis of SJS. The challenge with diagnosing DRESS on initial presentation is that several cutaneous adverse drug reactions have similar characteristics and lower DRESS incidence in children. However, having general knowledge of the syndrome and becoming familiar with the proposed criteria can aid in the prompt diagnosis. For instance, our case consisting of morbilliform components are not entirely consistent with SJS. Moreover, our patient presented with hepatitis which is much more consistent with DRESS and is rarely seen in SJS. This case also supports the ongoing research of the association of HHV-6 reactivation and DRESS syndrome. In conclusion, it would be advantageous for pediatricians to be aware of the diagnostic criteria of this potential life-threatening drug reaction and how to manage it.

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## Conflict of Interest

The authors declare that they have no potential conflicts of interest to disclose.

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## Patient Consent Statement

Patient consent was obtained. Institutional Review Board review is not required for this activity, for, as a case report, this work neither produces generalizable knowledge nor is it an investigation of a US Food and Drug Administration-regulated product.

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