

## A Morbilliform Rash After Sulfasalazine: A Case of DRESS Syndrome

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Received: April 29, 2020; Accepted: May 05, 2020; Published: May 12, 2020

### Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, drug-related reaction that should be suspected in the presence of fever, rash and systemic involvement after 2-8 weeks after exposure to a new drug. Here we report a case of a patient with DRESS syndrome after sulfasalazine.

**Keywords:** DRESS; Drug adverse reaction; Maculopapular exanthema; Drug rash

### 1. Introduction

Drug adverse reactions can have potentially life-threatening consequences. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) is a rare, drug-related reaction that should be suspected in the presence of fever, rash and systemic involvement (hematologic, hepatic, renal, pulmonary and cardiac) beginning after 2-8 weeks after exposure to a new drug [1]. The reported incidence rate ranges from 1:1000 to 1:10000. Different drugs are implicated in DRESS syndrome, especially anticonvulsant [2]. The pathogenesis of DRESS syndrome is not completely clear and interaction between different factors has been hypothesized, including a genetic deficiency of detoxifying enzymes with accumulation of drug metabolites [3], genetic associations between HLA and drug hypersensitivity [4-6], and virus-drug interaction, particularly for herpes viruses (HHV6, HHV7, EBV) and cytomegalovirus [7]. DRESS syndrome is a complex syndrome and standardized criteria for the diagnosis has been postulated, even if their utility is still to be validated [8]. Diagnosis is complex because of the variable presentations which can mimic a variety of other conditions, such as viral infections. Generally, fever precedes the skin reactions and the rash may progress to involve the entire body. The organ involvement (liver, heart, lung, kidney and colon) is the major cause of morbidity and mortality. Fever, skin reactions, particularly maculopapular lesions, abnormal liver functions tests and hematological findings are the most common features [9]. The prompt withdrawal of the drug is the first step in the management of DRESS syndrome, and still remains the true challenge

for clinicians. Supportive and symptomatic treatment are based on corticosteroids and in selected cases, immunomodulatory intravenous immunoglobulin [10,11]. Antiviral therapy is not suggested. Recurrent DRESS syndrome is possible and can be triggered by structurally unrelated drugs. Generally, recurrences are characterized by faster onset and limited to skin reactions. Allergological evaluation is strongly recommend before the initiation of new drugs.

## 2. Case Report

We report the case of a 48-year old man with unremarkable past medical history, who was admitted to our Emergency Department for flu-like syndrome (fever, discomfort, sore throat) and diffuse red macular papular lesions associated with increased liver enzymes, developed 4 weeks after administration of sulfasalazine. Sulfasalazine is a type of anti-inflammatory drug known as a disease-modifying anti-rheumatic drug (DMARD) [12]. He was hospitalized in the suspicion of severe drug reaction. The patient had been diagnosed with sieronegative arthritis at the beginning of June in another hospital and treated with corticosteroids and sulfasalazine at increasing doses for 4 weeks (maximum dose 2 g/day). Twenty-four days after the introduction of sulfasalazine, the patient developed fever and a rash on the neck. He immediately discontinued the medications. Liver enzymes were significantly increased (AST/ALT 165/257 U/mL, n.v. 10-37 U/L). He presented to our Emergency Department because he developed a morbilliform erythema on the upper trunk, arms and legs (FIG. 1 A, 1 B, 2, 3) and he complained sore throat.



FIG. 1. Morbilliform erythema on the upper trunk (A, front; B, back).



FIG. 2. Morbilliform erythema on the arms.



**FIG. 3. Morbilliform erythema on the legs.**

On admission, he had fever (38.0 °C) without chills and he presented a cutaneous rash with urticarial lesions on the trunk and maculopapular eruption on legs and arms, with oral mucosal involvement but no facial edema. Laterocervical lymphadenopathy was present. Blood pressure and EKG were normal. Ultrasound examination excluded visceral involvement and pleural/pericardial effusion. Chest X ray was normal. Empirical antibiotic therapy with amoxicillin clavulanate (1 gr q8h) was started.

Laboratory tests revealed hematological findings with activated lymphocytes and low platelet counts (126 000/mm<sup>3</sup>) with a mild increased CRP value (6.11 mg/dL, n.v. 0-0.5). Renal function was normal. Liver enzymes were confirmed increased with elevated ALT more than twice the upper limit of normal (211 U/L, n.v. 10-37).

Bacterial and viral infections, including viral hepatitis (HCV, HBV), HIV, CMV, EBV and Toxoplasma, were ruled out. Blood and urine cultures were negative and antibiotic therapy was discontinued as infectious etiology had been ruled out.

An allergological evaluation confirmed a toxic drug reaction. The delay between the drug exposure and the cutaneous rash, and the clinical presentation with fever and cutaneous lesions are consistent with the data reported in the literature, providing a strong support of sulfasalazine involvement.

According to the RegiSCAR criteria for the diagnosis of DRESS (hematological abnormalities, liver involvement and systemic symptoms) [13], we started methylprednisone at increasing doses (maximum dose 1 mg/Kg/day). The cutaneous rash quickly improved and no vesicles, bullae nor target lesions appeared, so we decided not to check HHV-6 and HHV-7. Fever and sore throat completely resolved in few days. Liver enzymes continued to rise up with ALT>AST (respectively, 1382 U/L and 379 U/L) and an abdomen ultrasound was performed, excluding cholecystitis and focal lesions.

He was discharged on an oral prednisone 1 mg/Kg/day with a planned taper and a short-term follow-up. Skin reaction quickly improved, while liver enzymes slowly decreased in 3 weeks. A multidisciplinary approach with combined allergological and rheumatological evaluation was planned. Corticosteroid was administered with a tapering strategy for 3 weeks until complete resolution of skin lesions and normal liver enzymes.

### **3. Discussion**

Drug reactions can have severe consequences, including death in the most severe cases. Many patients can be affected by chronic skin and mucosal sequelae, which can impair the quality of life. Practitioners and patients need to be aware of the initial symptoms and signs of drug adverse reactions, including fever, cutaneous reactions and mucosal involvement. Early drug withdrawal is the most important measure in the clinical practice and it remains the best way to improve the prognosis. Systemic corticosteroid is currently the most widely accepted treatment, but the optimal dose and the duration therapy are unknown.

### **4. Conflict of Interest**

The authors declare that they have no conflict of interest.

### **5. Author Contribution**

EP: is responsible for investigation, writing and editing the original draft. GL: is responsible for assisting in editing and review. AV: is responsible for the data collection and assisting in editing and review.

### **6. Ethical Approval**

Full consent has been given by the patient for publication of the case report.

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