

## DRESS Syndrome: Patch Testing as a Diagnostic Method That Brings Us Closer to a Definitive Result

García-Paz V, González-Rivas M, Otero-Alonso A  
*Allergy Department, Santiago de Compostela University Hospital,  
Santiago de Compostela, Spain*

*J Investig Allergol Clin Immunol* 2022; Vol. 32(2): 159-160  
doi: 10.18176/jiaci.0728

**Key words:** DRESS syndrome. Amoxicillin allergy. Penicillin allergy. Patch test.

**Palabras clave:** Síndrome de DRESS. Alergia a amoxicilina. Alergia a penicilina. Pruebas epicutáneas.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a drug hypersensitivity reaction characterized by the appearance of exanthematous lesions with fever and systemic involvement [1]. The incidence of DRESS syndrome in Spain is around 3.89 cases per 10 000 patients [2].

Anticonvulsants, antibiotics, and allopurinol are the most commonly implicated drugs [2]. The interaction between genetic, immunological, metabolic, and pharmacokinetic factors, as well as reactivation of a viral infection (Epstein-Barr virus [EBV], cytomegalovirus [CMV], human herpesvirus [HHV] 6, HHV-7) [3], seems to be involved in pathogenesis. DRESS syndrome is considered a delayed drug reaction, with the most frequently reported latency period varying from 2 to 6 weeks after the first administration of the culprit drug. However, latency periods shorter than 15 days and longer than 105 days have been reported [2,4-6]. In the case of re-exposure to the same culprit drug, symptoms may even develop within 24 hours [3,7].

A wide range of symptoms involving various organs and systems may be present, with high fever (38-40°C) being the most common clinical manifestation [2]. Skin lesions are common, mainly morbilliform exanthem or macular erythema progressing to a violaceous and subsequently exfoliative picture. The mucous membranes and genitals, however, are rarely affected. Bilateral lymphadenopathy is the third most frequent clinical manifestation. Also frequent are eosinophilia and other hematological abnormalities, such as atypical lymphocytes [8]. Moreover, 50% to 80% of patients develop liver dysfunction, which is the main cause of death in those whose progress is poor, although other organs may also be affected [2]. Up to 10% of patients with DRESS syndrome die [6].

Diagnosis is challenging due to the variability of the clinical manifestations, the wide group of diseases that must be taken into account in the differential diagnosis, and the absence of specific diagnostic tests. According to the European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) [5], the presence of 4 out of the 7 independent parameters included is strongly suggestive of the diagnosis. The gold standard test would involve re-exposure to the drug. However, this

is not recommended for ethical reasons (it could provoke a life-threatening reaction). Patch testing is a safe and useful alternative for demonstrating drug-specific nonimmediate hypersensitivity [9]. Supportive and symptomatic measures are the only treatment once the culprit drug has been discontinued, although recovery can take several weeks. We report a case of DRESS syndrome due to amoxicillin where patch tests proved useful as a diagnostic tool.

A 26-year-old man was referred to our service for suspected penicillin allergy. In May 2020, his dentist had prescribed oral amoxicillin 1 g 3 times a day as prophylaxis following a dental procedure; 6 hours after the third pill, he developed facial erythema and labial angioedema that progressed during the night to micropapular lesions with vibrant red erythema that later became purplish and affected the entire body surface. He also presented bilateral lymphadenopathy in the laterocervical area and fever up to 39°C.

The patient himself decided to stop treatment and, given the pandemic situation, underwent polymerase chain reaction assay for SARS-CoV-2. The result was negative. Complete laboratory tests and serology for EBV were requested by his physician after a telephone call, although no biopsy was performed.

Transaminases were elevated (aspartate aminotransferase, 97 IU/L [normal range 10-40]; alanine aminotransferase, 109 IU/L [normal range, 3-41]), with eosinophilia 9% and an absolute eosinophil count of 690/ $\mu$ L (baseline values within normal ranges were verified in previous and subsequent tests for all parameters). Despite being treated with antihistamines and corticosteroids, the reaction took 3 weeks to resolve and was characterized by generalized desquamation, especially in the genital area and on the palms and soles. Five months after the reaction the patient attended our Allergy Department, where he showed us images of the lesions taken by himself (Supplementary Figure).

At his first visit, and after giving his informed consent, skin prick tests (SPTs) and intradermal tests (IDTs) were performed with benzylpenicilloyl polylysine, sodium benzylpenicilloate (Diater Laboratory), penicillin G (SPT, 10 000 IU; IDT, 10 000 IU), ceftriaxone, cefuroxime (both SPT, 20 mg/mL; IDT, 2 mg/mL), and meropenem (1 mg/mL). All results were immediately negative. Twenty-four hours later, a positive delayed reaction was detected with penicillin G. Ampicillin, amoxicillin, and amoxicillin-clavulanic acid had not been tested because they were involved in the reaction [10]. Given the likelihood of DRESS syndrome (RegiSCAR score, 5), and in order to complete the study, the patient underwent patch testing 15 days after the first visit with amoxicillin 10% pet, amoxicillin 5% aq, and ampicillin 5% aq and pet. The results were positive at 48 and 96 hours (Figure). Antigens at different concentrations and vehicles were tested at the same visit, although successive visits to the hospital were not recommended during the COVID-19 pandemic. Finally, to rule out various etiologies of DRESS syndrome, the patient underwent serology testing (EBV, CMV, and HHV-6), which was negative. The patient was diagnosed with DRESS syndrome due to amoxicillin.

Given that guidelines recommend controlled exposure tests with an alternative  $\beta$ -lactam if the benefit outweighs the risk



**Figure.** Patch test with amoxicillin 10% pet and 5% aq and ampicillin 5% aq and pet at 96 hours showing positive results.

and monitoring of temperature and laboratory values [2], we explained the procedure to the patient and performed an oral graded challenge test with cefuroxime. The result was negative.

The interest in the singular case we present lies in its specific features. First, symptoms appeared early, and this seems to be associated with the previous exposure to the culprit drug. In fact, some authors have suggested that these criteria should be revised [5,6]. Second, the present report highlights the importance of the allergology study, which could add valuable information (eg, the role of a specific drug), supported by positive skin test results and the evaluation of alternative drugs to be used in the future. Finally, DRESS syndrome requires high diagnostic suspicion, and its prognosis is directly proportional to the time of exposure to the culprit drug [4]. In the present case, the patient himself stopped treatment, demonstrating that rapid diagnosis with early cessation of the drug reduces the severity of the reaction.

#### *Funding*

The authors declare that no funding was received for the present study.

#### *Conflicts of Interest*

The authors declare that they have no conflicts of interest.

## References

1. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med Surg.* 1996;15(4):250-7.
2. Cabañas R, Ramírez E, Sendagorta E, Alamar R, Barranco R, Blanca-López N, et al. Spanish Guidelines for Diagnosis, Management, Treatment, and Prevention of DRESS Syndrome. *J Investig Allergol Clin Immunol.* 2020;30(4):229-53.
3. Míguez-Martín L, Higuelmo-Gómez H, Gómez-Farpón Á, Álvarez-Caro F. Delayed aminopenicillin reaction associated to human herpes virus 6 infection mimicking DRESS syndrome. *Rev Alerg Mex.* 2019;66(3):375-8.
4. Mori F, Caffarelli C, Caimmi S, Bottau P, Liotti L, Franceschini F, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) in children. *Acta Biomed.* 2019;90(3-5):66-79.
5. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol.* 2013;169(5):1071-80.
6. Sandhu S, Neema S, Vashisht D, Venugopal R, Sengupta P, Radhakrishnan S. Drug reaction with eosinophilia and systemic symptoms: A single center descriptive observational study. *Dermatol Ther.* 2021;34(1):e14670.
7. Soria A, Bernier C, Veyrac G, Barbaud A, Puymirat E, Miliped B. Drug reaction with eosinophilia and systemic symptoms (DRESS) may occur within two weeks of drug exposure: a retrospective study. *J Am Acad Dermatol.* 2020;82(3):606-11.
8. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. *Allergol Int.* 2019;68(3):301-8.
9. Santiago F, Gonçalo M, Vieira R, Coelho S, Figueiredo A. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). *Contact Dermatitis.* 2010;62(1):47-53.
10. Dua, S, Nasser S, Ewan P. Reactivation of DRESS syndrome by intradermal tests. *Allergy.* 2011;66(SUPPL.94):86.

■ *Manuscript received March 16, 2021; accepted for publication June 28, 2021.*

**Andrea Otero Alonso**

Servicio de Alergología  
Complejo Hospitalario Universitario de Santiago  
Santiago de Compostela, Spain  
E-mail: andrea.otero.alonso@sergas.es