DRESS Syndrome: Patch Testing As a Diagnostic Method That Brings Us Closer to a Certain Result

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Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) is a drug hypersensitivity reaction characterized by the appearance of exanthematous lesions with fever and systemic involvement [1]. DRESS incidence 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 among genetic, immunological, metabolic and pharmacokinetic factors, as well as reactivation of a virus infection (EBV, CMV, HHV-6, HHV-7)[3] seems to be involved in its pathogenesis. DRESS is basically considered a delayed drug reaction and the most commonly notified latency period varies between 2 to 6 weeks after the first administration of the culprit drug. However, latencies shorter than 15 days and longer than 105 days have been reported [2,4-6]. Besides, in case of re-exposures to the same culprit drug, symptoms even may develop within 24 hours [3,7].

A wide range of symptoms involving various organs and systems may be present, being high fever (38-40ºC) the most common clinical manifestation [2]. Regarding skin lesions a morbilliform exanthema or macular erythema that may evolve to violaceous and later become exfoliative are commonly seen. On the contrary, mucous membranes or genitals are rarely affected. Finally, the presence of bilateral lymphadenopathy is the third most frequent clinical manifestation. Eosinophilia and other hematological alterations such as atypical lymphocytes are frequently found [8]. Moreover, fifty to 80% of patients develop

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liver disfunction, being the main cause of mortality in those with poor evolution, although other organs can be affected as well [2].The calculated mortality rate of the disease is up to 10%[6].

Diagnosis is a challenge due to the variability of its clinical manifestations and the wide group of diseases that must be taken into account in its differential diagnosis, as well as the absence of specific diagnostic tests. According to RegiSCAR [5] (European Registry of Severe Cutaneous Adverse Reactions to Drug and Collection of Biological Samples), the presence of 4 out of the 7 independent parameters included, strongly suggests the diagnosis. Even though the gold standard test would be re-exposure to the drug, it could provoke a life-threatening reaction and it is not recommended for ethical reasons. Alternatively patch test could be a safe and useful procedure to demonstrate a drug-specific non-immediate hypersensitivity [9]. Supportive and symptomatic measures are the only treatment once the culprit drug has been discontinued, but recovery can take several weeks. A case of DRESS due to amoxicillin where patch tests were proven as a useful diagnostic tool is presented.

A 26-year-old male, pharmacist, was referred to our service for suspected penicillin allergy. In May 2020, his dentist prescribed oral Amoxicillin 1g TID as preventive treatment for a dental procedure; 6 hours after the third pill, he presented facial erythema and labial angioedema that progressed during the night to micro-papular lesions with erythema over the entire body surface in a vibrant red color that later became purplish. He also presented bilateral lymphadenopathy in the laterocervical area and fever of up to 39ºC.

The patient himself decided to stop treatment and, due to the current pandemic situation, a screening with SARS CoV2 PCR was done with a negative result. Complete laboratory tests and EBV serology were requested by his physician after a telephone call and no biopsy was performed.

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Transaminase elevation was observed (GOT 97UI/L normal range 10-40; GPT 109 UI/L normal range 3-41) and eosinophilia 9%, absolute eosinophilia 690uL (baseline values within normal ranges were verified in previous and subsequent tests for all parameters). Despite of being treated with antihistaminic and corticosteroids, the reaction took to resolve 3 weeks with generalized desquamation, especially in the genital, and hands and sole area. 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 and intradermal tests with benzyl penicilloylpolylysine, sodium benzylpenicilloate (Diater Laboratory, Madrid, Spain), penicillin G (prick 10.000UI, ID 10.000UI), ceftriaxone, cefuroxime (both prick 20mg/mL, ID 2mg/mL), and meropenem (1 mg/mL) were done with immediate negative results. Twenty-four hours later, a positive delayed reaction was detected with penicillin G. Ampicilin, Amoxicillin and Amoxicillin-clavulanic acid had not been tested because they were involved in the reaction [10]. Because of the probable DRESS (RegiSCAR score 5), and in order to complete the study, fifteen days after the first visit, epicutaneous tests with Amoxicillin 10% pet, Amoxicillin 5% water, Ampicillin 5% water and pet were done with positive results at 48- and 96-hour readings (Figure 1). Antigens on different concentrations and vehicles were tested at the same time although not recommended for safety reasons, to avoid successive visits to the hospital during the COVID-19 pandemic. Finally, to rule out different etiologies of DRESS, negative virus serologies (EBV, CMV and VVH-6) were obtained. The patient was diagnosed with DRESS Syndrome due to Amoxicillin.

Taking into account that controlled exposure tests with an alternative beta-lactam is recommended in guidelines if the benefit outweighs the risk and with temperature and

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analytical surveillance (2)and after explaining the procedure to the patient, an oral graded challenge test with Cefuroxime was carried out with no reaction.

The interest in this singular case lies in a few of specific features. Firstly, the early appearance of symptoms, which seems to be likely related to the previous exposure to the culprit drug. In fact, some authors have suggested that these criteria should need further revision [5,6]. Secondly, the present report highlights the importance of the allergological study, which could add valuable information such as the role of a specific drug supported by positive skin tests and the study of alternative drugs to be used in the future. Finally, DRESS syndrome requires a high diagnostic suspicion and its prognosis is directly proportional to the time of exposure to the culprit drug [4]. In our case, the patient himself stopped the treatment, demonstrating that an early diagnosis with an early cessation of the drug reduces the severity of the reaction.

Conflict of interest

The authors declare no conflicts of interest.

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Compliance with ethical statements

Inform consent was obtained from the participant included in the study.

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Figure Legend

Figure 1. Epicutaneous patch test with Amoxicilin 10% pet and 5% water, Ampicilin 5% water and pet reading at 96 hours with positive results.

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