

Drug reaction with eosinophilia and systemic symptoms (DRESS): a diagnostic and treatment challenge

Reação a drogas com eosinofilia e sintomas sistêmicos (DRESS): desafio no diagnóstico e tratamento

Dina Larissa Capelasso da Costa¹, Débora Mutti de Almeida Monteiro¹,
Thábata Chiconini Faria¹, Ana Flávia Faria de Camargos¹, Veridiana Aun Rufino Pereira¹,
Maria Elisa Bertocco Andrade¹, Fátima Rodrigues Fernandes¹

ABSTRACT

Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a serious disease. Its severity is related to the degree of visceral involvement and its mortality rate is approximately 10%. Diagnosis is a challenge, although RegiSCAR scores can facilitate the process. **Objective:** To analyze clinical and laboratory data, clinical course, and classify cases according to RegiSCAR scores among patients diagnosed with DRESS who were admitted to the Allergy and Immunology service of the Hospital do Servidor Público Estadual de São Paulo. **Method:** This retrospective study analyzed the medical records of patients seen between January 2006 and January 2020. **Results:** There was a higher prevalence of women, with DRESS mainly affecting adults and older adults; cardiovascular diseases were the most frequent comorbidity. The most common clinical symptom was fever (69.2%), while the most common laboratory finding was eosinophilia. The most frequent skin lesion was maculopapular rash, and anticonvulsants were the main prescribed drug class. The drug was used for a mean of 2.1 weeks, and all patients received systemic corticosteroids as the main treatment. Human immunoglobulin was used as an additional treatment in 3 patients. Mortality was 7% in the acute phase and 14% due to secondary causes. **Conclusion:** DRESS is a severe, complex, and potentially fatal syndrome whose diagnosis is challenging. RegiSCAR scores helped confirm diagnosis and differentiate it from other diseases. The disease's mortality highlights its severity. Recognizing and excluding the implicated drug and initiating early treatment led to a greater chance of survival for these patients.

Keywords: Eosinophilia, anticonvulsants, drug hypersensitivity, drug hypersensitivity syndrome.

RESUMO

Introdução: A reação a medicamentos com eosinofilia e sintomas sistêmicos (DRESS) trata-se de uma doença grave, sendo sua gravidade relacionada ao grau de acometimento visceral, e sua taxa de mortalidade de cerca de 10%. Seu diagnóstico é desafiador, e a utilização do escore RegiSCAR como ferramenta facilita a formação deste diagnóstico. **Objetivo:** Analisar os aspectos clínicos, laboratoriais, evolução e classificação dos casos segundo o RegiSCAR dos pacientes internados no serviço de Alergia e Imunologia do Hospital do Servidor Público Estadual de São Paulo, com o diagnóstico de DRESS. **Método:** Trata-se de um estudo retrospectivo baseado na análise de prontuários de pacientes atendidos no período entre janeiro de 2006 a janeiro de 2020. **Resultados:** Neste estudo verificou-se maior prevalência do sexo feminino, e a DRESS acometeu principalmente adultos e idosos, tendo como comorbidades mais frequentes as doenças cardiovasculares. Dos sintomas clínicos, 69,2% dos pacientes apresentava febre, e a alteração laboratorial mais encontrada foi a presença de eosinofilia. A lesão cutânea mais frequente foi o exantema maculopapular, e os medicamentos, os anticonvulsantes. O tempo prévio de uso do medicamento foi de 2,1 semanas, e todos os pacientes receberam corticoide sistêmico como tratamento principal, e 3 pacientes fizeram uso da imunoglobulina humana como tratamento adicional. A mortalidade foi de 7% na fase aguda, e 14% por causas secundárias. **Conclusão:** A DRESS é uma síndrome complexa grave e potencialmente fatal, cujo diagnóstico é desafiador. O uso do escore preconizado pelo RegiSCAR demonstrou ser importante auxílio na confirmação do diagnóstico e na diferenciação de outras doenças. A mortalidade encontrada destaca a gravidade da doença. Reconhecer e excluir a droga implicada e iniciar um tratamento precoce permite maior chance de sobrevivência para estes pacientes.

Descritores: Eosinofilia, anticonvulsantes, hipersensibilidade a drogas, síndrome de hipersensibilidade a medicamentos.

1. Hospital do Servidor Público Estadual de São Paulo, Allergy and Immunology Fellowship Program - São Paulo, SP, Brazil.

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe type of cutaneous adverse drug reaction characterized by rash, fever, leukocytosis with eosinophilia and/or atypical lymphocytes, lymph node enlargement, and renal and/or hepatic dysfunction. Its incidence is 1 in 1,000 to 1 in 10,000 drug exposures.^{1,2} DRESS severity is often related to the degree of visceral involvement and its mortality, which has a rate of 10%. Identifying the condition early to start specific treatment as soon as possible is of utmost importance.³

The pathogenesis of DRESS is only partially understood and involves different mechanisms, such as detoxification defects leading to reactive metabolite formation and subsequent immunological reactions, slow acetylation, and reactivation of human herpes.⁴

Symptom onset typically occurs after 2 weeks of medication use. Clinical characteristics of the disease include multiorgan involvement and often signs of clinical worsening such as fever, rash, and renal and hepatic dysfunction, occurring even after discontinuation of the medication.^{4,5} Anticonvulsants and allopurinol are the most common causes of DRESS, and the main treatment consists of withdrawing the offending medication and starting systemic corticosteroids.⁶

Diagnosis is challenging, as the different signs and symptoms of DRESS are also observed in other serious conditions with similar characteristics. Therefore, an international study group called RegiSCAR developed a score based on patients' clinical condition and additional laboratory/histopathological data that classifies the diagnosis of DRESS as definitive, probable, possible, or negative (Table 1).^{2,4,6}

Objective

This study aimed to assess clinical and laboratory data, as well as the evolution and classification of patients with suspected DRESS admitted to the Allergy and Immunology service of the Hospital do Servidor Público Estadual de São Paulo, Brazil, according to the RegiSCAR criteria.

Population and methods

This was an observational, descriptive, retrospective, and prospective study with data from patient records

Table 1

RegiSCAR criteria for potential DRESS cases

| |
|---|
| (1) Hospitalization |
| (2) Reaction suspected to be drug-related |
| (3) Acute rash |
| (4) Fever > 38 °C |
| (5) Enlarged lymph nodes involving at least 2 sites |
| (6) Involvement of at least 1 internal organ |
| (7) Blood count abnormalities |
| – Lymphocytes above or below reference intervals |
| – Eosinophils above references intervals |
| – Platelet count below reference intervals |

DRESS = drug reaction with eosinophilia and systemic symptoms.

RegiSCAR = registry of severe cutaneous adverse reactions.

Fonte: Kardaun SH, et al.⁴.

and databases. Patients with suspected DRESS who were classified as possible, probable, or definitive DRESS according to the RegiSCAR score treated at Hospital do Servidor Público Estadual de São Paulo – Francisco Morato de Oliveira from January 2006 to January 2020 were included in the study. There was no age restriction. Patients were analyzed according to age, sex, suspected drug, presence of fever, peripheral eosinophilia (> 500), presence of atypical lymphocytes, involvement of other systems, skin manifestations, treatment, complications/sequelae, and mortality.

After collection, data were analyzed using descriptive statistics. Variables were expressed in absolute and relative frequencies and subsequently compared with the literature.

The study was approved by the Research Ethics Committee of Hospital do Servidor Público Estadual (protocol number 25595419.9.0000.5463) on June 03, 2020, under consolidated opinion number 4.067.426. Because the study used retrospective data from medical records and preserved patient anonymity, informed consent was waived.

Results

Initially, a total of 57 patients with suspected DRESS were identified. After the RegiSCAR score was applied, and based on clinical and laboratory data from medical records, 5 patients were classified as negative and were excluded from the study. The remaining 52 patients were included, of whom 19 were classified as possible, 19 as probable, and 14 as definitive cases.

Patient age ranged from 5 to 89 years, with a mean age of 54.9 and a median age of 61 years. DRESS mostly affected those aged > 45 years and older patients (Figure 1). Twenty-seven (52%) patients were women and 25 (48%) were men. Forty-two patients had one or more associated comorbidities – the most common was cardiovascular disease (44.2%), followed by endocrinopathies (38.4%), current neoplasms (21.1%), nephropathies (13.4%), atopy (7.6%), rheumatologic disease (5.7%), mental disorders (5.7%), epilepsy (3.8%), and chronic bowel disease (1.9%) (Table 2).

Fifty-one patients had laboratory tests described in their medical records, which included the following alterations: eosinophilia in 74.5%, atypical lymphocytes in 19.6%, liver dysfunction in 66.7%, and renal dysfunction in 36.7%. In systemic involvement assessment, of 52 patients, 36 (69.23%) had fever. Of the analyzed patients, 72.4% had low immunoglobulin levels during the DRESS episode

(Table 3). Thirty-nine patients had skin manifestations – maculopapular rash was the most common (74.4%), followed by erythroderma desquamativum in 12.8%, bullous pemphigoid in 5.1%, pustular rash in 5.1%, and erythematous-violaceous patches in 2.6% (Figure 2).

The suspected cause of DRESS was a drug class in 40 patients. Anticonvulsants were the most prevalent (17), followed by antibiotics (15), nonsteroidal anti-inflammatory drugs (4), xanthine oxidase inhibitors (2), antiretrovirals (1), and minocycline (1). Analysis of isolated and concomitant drug therapy showed that antibiotics was the most prevalent class, and the most common group among them was beta-lactams (Table 4). Mean time of medication use prior to DRESS onset was 2.1 weeks. In addition to withdrawing the suspected medication, all patients were treated with corticosteroids. Only 3 patients received intravenous immunoglobulin combined with corticosteroid treatment.

Of the analyzed patients who died, the cause of death was acute DRESS in 4 (7%) and secondary causes in 8 (14%) (Figure 3). All patients who died had one or more comorbidities associated with DRESS.

At clinical follow-up, 12 patients were scheduled to perform a patch test to identify the offending medication, but only 3 (5.7%) attended the appointment. The suspected medication was confirmed in two patients

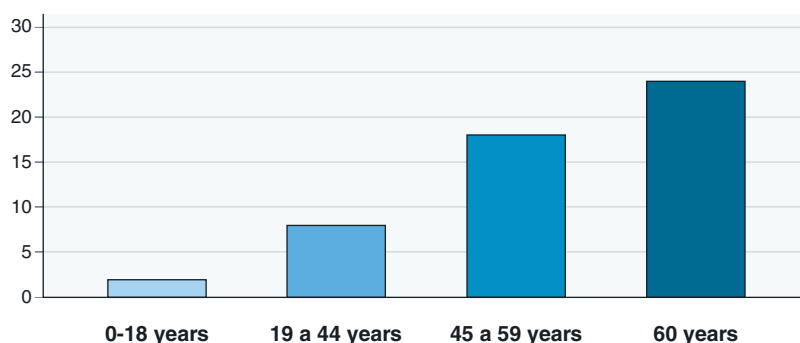


Figure 1
Patient distribution by age group

Table 2

Analysis of patient comorbidities

| Comorbidities | | N | % |
|------------------------|---------------------------|----|-------|
| Cardiovascular disease | SH | 18 | 34.6% |
| | Arrhythmia | 1 | 1.9% |
| | SH + arrhythmia | 2 | 3.8% |
| | SH + heart failure | 1 | 1.9% |
| | SH + dyslipidemia | 1 | 1.9% |
| Endocrinopathies | Diabetes | 11 | 21.1% |
| | Hypothyroidism | 3 | 5.7% |
| | Diabetes + hypothyroidism | 6 | 11.5% |
| Neoplasms | Brain neoplasms | 8 | 15.3% |
| | Other neoplasms | 3 | 5.7% |
| Nephropathies | | 7 | 13.4% |
| Atopy | | 4 | 7.6% |
| Rheumatologic disease | | 3 | 5.7% |
| Mental disorders | | 3 | 5.7% |
| Epilepsy | | 2 | 3.8% |
| Chronic bowel disease | | 1 | 1.9% |

SH = systemic hypertension.

(1 positive for carbamazepine and 1 for amoxicillin), whereas the third patient tested negative for the suspected medication.

Discussion

In this study, 36.5% of patients were classified as possible cases, 36.5% as probable cases, and 27% as definitive cases. Cacoub et al. identified 20% of possible cases, 45% of probable, and 27% of definitive, whereas Kardaun et al. found 56 possible cases, 59 probable cases, and 59 definitive cases. This variation may be explained by the diagnosis being dependent on medical knowledge. Most doctors are not familiar with DRESS, which may hinder early notification and laboratory testing, as some test

Table 3

Laboratory test alterations in patients

| Laboratory findings | % |
|------------------------------------|--------------|
| Atypical lymphocytes | 19.6% |
| Eosinophilia | 74.5% |
| Altered liver function | 66.7% |
| Altered kidney function | 36.7% |
| Reduced immunoglobulin (Ig) levels | Total: 72.4% |
| | IgM: 51.7% |
| | IgG: 24.1% |
| | IgA: 17.2% |

Table 4
Medications associated with DRESS

| Drug class | Medication | N |
|-------------------------------------|---------------|----|
| Anticonvulsants (17) | Phenytoin | 6 |
| | Carbamazepine | 6 |
| | Phenobarbital | 2 |
| | Others | 5 |
| Antibiotics (15) | Beta-lactams | 18 |
| | Sulfonamide | 3 |
| | Others | 5 |
| NSAIDs (4) | Dipyron | 11 |
| | Others | 4 |
| Xanthine oxidase inhibitors | | 2 |
| Other isolated medication | | 2 |
| Antibiotics + NSAIDs | | 9 |
| Other concomitant drugs (2 or more) | | 3 |

NSAID = nonsteroidal anti-inflammatory drugs.

DRESS = drug reaction with eosinophilia and systemic symptoms.

alterations are only relevant during the first days of onset. Furthermore, the recognition of the condition and complete collection of clinical and laboratory data are often complex, which can lead to confusion and delay the diagnosis.^{1,4}

Patient age ranged from 5 to 89 years, with a mean age of 54.98 years, and 52% were women. According to Cabaña et al., DRESS can also occur in children, but mostly affects adults and has no gender predilection.⁹ However, Kaurdaun et al. found a predominance of the female sex, as well as Perelló et al., who observed a higher rate of adverse drug reactions in women. This may be explained by the fact that women seek health services more often and take more medication than men.^{4,10}

In the study by Kardaun et al., most patients had seizure disorders (20%), followed by diabetes (12%), cardiovascular disease (8.5%), previous

kidney disease (6%), liver disease (5.1%), and recent cancer (5.1%). In our study, the most common comorbidity was cardiovascular disease (44.2%),⁴ but endocrinopathies were also coincidentally the second most common. We found a higher prevalence of associated comorbidities than other studies, which could be explained by the greater number of adults and older adults included in the sample. These age groups tend to present more comorbidities, especially diseases of the cardiovascular system.¹¹ Oliveira and Moraes Jr. explain that the greater the number of comorbidities, the greater the number of medications being used and, consequently, the greater the chances of DRESS.¹²

When evaluating systemic involvement, 69.2% of patients had fever, which is considered one of the most common signs of DRESS.⁸ In the study by Kardaun et al., 90% of patients with DRESS had fever.⁴

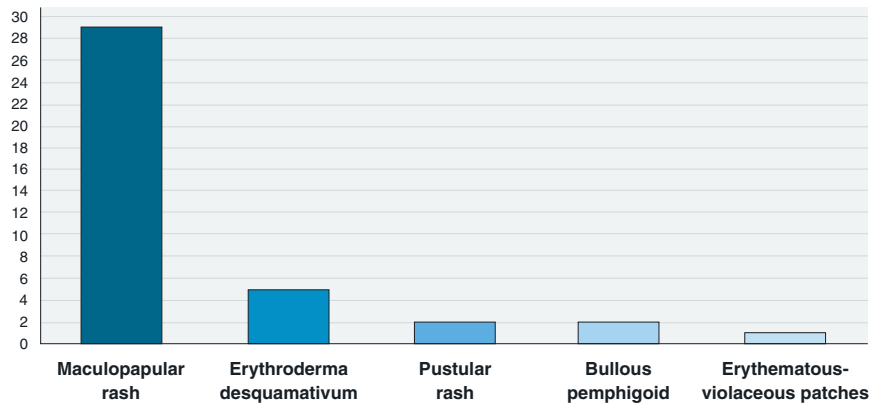


Figure 2
Distribution of skin lesions

Regarding laboratory alterations, 19.6% of patients had atypical lymphocytes, 74.5% had eosinophilia, 66.7% had altered liver function, and 36.7% had altered renal function. Of analyzed patients, 72.4% had decreased immunoglobulin levels during the DRESS episode. These values are similar to those reported by Cho et al.: eosinophilia in 66%-95% of cases, atypical lymphocytes in 27%-67%, liver alterations in 75%-94%, and renal alterations in 12%-40%. They also reported that some studies have demonstrated the presence of transient hypogammaglobulinemia during the initial stages of DRESS due to a decrease in B lymphocytes during this period.⁵

Watanabe and Gouveia et al. reported that the lesion most commonly associated with DRESS is maculopapular rash, which is in accordance with the 74.4% rate of maculopapular rash found in this study.^{8,13}

Anticonvulsants, when used alone, were the most common class of drugs implicated in DRESS in this study, as well as in the studies by Kardaun et al.⁴ and Cacoub et al.¹ In these same studies, the most prevalent anticonvulsant was carbamazepine, which was also one of the most prevalent in our study, as well

as phenytoin. Ang et al. reported a high prevalence of phenytoin among offending medications.¹⁴ Perello et al. also found anticonvulsants to be the main offending

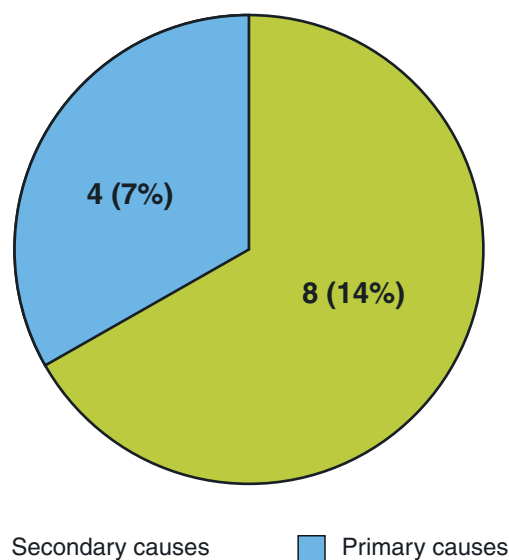


Figure 3
Patients who died due to primary or secondary causes

drug class when assessing serious adverse drug reactions, followed by beta-lactam antibiotics.¹⁰

Antibiotics were the second most common drug class. Kardaun et al. found a 25% prevalence of antibiotics (12% sulfonamide and 13% other antibiotics), with sulfonamide being the most common, but in our study the most prevalent class was beta-lactams.⁴ A possible cause for the higher prevalence of beta-lactams is the fact that these are the most commonly used class of antibiotics today.¹⁵ Cacoub et al. observed delayed symptom onset, typically 2 to 6 weeks after using the medication.¹ Kano et al. also reported that DRESS symptoms typically appear 2 weeks after starting the medication.¹⁶ In this study, we found a mean time of medication use prior to DRESS onset of 2.1 weeks. Regarding treatment, all patients received systemic corticosteroids at an initial dose of approximately 1 mg/kg/day, and only 3 patients received immunoglobulin in association with corticosteroids. According to Ferreira et al., first-line treatment (concomitantly with withdrawal of the medication) consists of systemic corticosteroids at a dose of 0.5 to 1 mg/kg/day, with gradual dose reduction, and immunoglobulin, which should not be used as monotherapy in cases of DRESS. However, the use of immunoglobulin is controversial because of possible adverse effects.^{1,3}

We found a DRESS mortality rate of 7%, similar to the rate of 2%-14% found by Watanabe.⁸ Cacoub et al. also found a mortality rate of approximately 10%.¹

Conclusion

In this study, DRESS most commonly affected women, adults, and older adults, and the most common comorbidity was cardiovascular disease. Fever was the most prevalent clinical manifestation, and eosinophilia was the most frequent laboratory alteration.

The predominant cutaneous manifestation was maculopapular rash, and anticonvulsants, when used alone, were the main class of drugs implicated in DRESS. Mean time of medication use prior to DRESS onset was 2.1 weeks, and all patients received systemic corticosteroids as the main treatment. Only 3 patients received human immunoglobulin as an additional treatment.

In conclusion, DRESS is a severe and potentially fatal complex syndrome whose diagnosis is challenging. The RegiSCAR score was shown to

be an important aid in confirming the diagnosis and differentiating it from other diseases. The mortality rate highlights the severity of the condition. Identifying and withdrawing the offending medication, as well as starting treatment early, has a key role in patient recovery.

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Corresponding author:
Dina Larissa Capelasso da Costa
E-mail: larissacapelasso@gmail.com