

DRESS syndrome: an unlikely diagnosis with an unlikely cause

Sofia Garcês Soares, MD, MSc^{a,*}, M. H. Mendes, MD, MSc^a, P. Pinto-Lopes, MD, MSc^{a,b}

Abstract

Drug reaction with eosinophilia and systemic symptoms syndrome is a rare and severe adverse drug reaction which is potentially life-threatening. We report a case of a 66-year-old male, with no prior history of allergies, who went to the emergency department with fever, headache and a rash, 12 days following receiving metronidazole for 7 days. He had no recent trips, contact with sick people or animals. The authors aim to alert to an uncommon and serious syndrome caused by an unlikely drug.

Keywords: DRESS syndrome, drug, rash

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome also known as drug-induced hypersensitivity syndrome (DIHS) is a rare and severe adverse drug reaction.¹ The culprit drugs vary and its manifestations generally develop 2 to 6 weeks after starting therapy.¹ It is characterized by fever, cutaneous eruption and multiorgan involvement, being the liver the most frequent involved.¹⁻³ The authors aim to alert to a serious and rare pathology with an unlikely cause, in an attempt to contribute to an earlier diagnosis and outcome improvement.

Case report

A 66-year-old male, without significant past medical history and no known allergies, went to the emergency department complaining of fever, headache, and an erythematous rash with 5 days of evolution. He denied recent trips, contact with sick people, having animals or any recent drugs. On physical examination, he presented a diffuse erythematous rash (Fig. 1), without pruritus, petechiae, enanthem, or adenopathies; BP 86/55 mm Hg, HR 81 bpm, SpO₂ 95% (FiO₂ 21%), and fever. The cardiopulmonary examination revealed diffuse pulmonary crackles on auscultation. The neurological, abdominal and genitourinary examination were unremarkable.

The blood gas analysis showed mild hypocapnia without hypoxemia. The initial laboratory assessment revealed mild leukocytosis ($13.62 \times 10^3/\mu\text{L}$) with neutrophilia ($11.73 \times 10^3/$

μL) and eosinophilia ($1.02 \times 10^3/\mu\text{L}$) and elevated C-reactive protein (148.3 mg/L); all the other blood tests requested were normal, namely: hemoglobin and platelet counts, coagulation tests, liver function tests, renal function, electrolytes and urinalysis/urine sediment.

The patient was admitted to the Internal Medicine ward due to a febrile syndrome and diffuse macular rash/erythroderma in an immunocompetent patient.

A broad laboratory assessment was made, revealing: worsening of eosinophilia ($1.81 \times 10^3/\mu\text{L}$) and transaminases (AST210UI/L and ALT 213UI/L). Procalcitonin (0.39ng/mL) and erythrocyte sedimentation rate (29mm/h) were mildly elevated. The immuno-logical study revealed negative anti-dsDNA, anti-extractable nuclear antigens and anti-neutrophil cytoplasmic antibodies; angiotensin converting enzyme level was normal (<8U/L). Immunoglobulin levels (IgA, IgM, IgG) were normal, without complement consumption. Protein electrophoresis showed mild elevation of alpha globulins. Urine and blood cultures were sterile; antistreptolysin O titer was normal. Viral markers of HIV 1/2, HBV and HCV were negative; EBV, CMV and *Mycoplasma pneumoniae* IgG seropositivity was evidenced.

Due to the pulmonary changes on auscultation, it was requested a thorax computed tomography (CT) scan which evidenced pulmonary micronodules and mediastinal lymph nodes. It was then performed a bronchofibroscopy which displayed a hyperemic mucosa and bronchoalveolar lavage (BAL) was subsequently done. Ziehl-Neelsen stain and myco-bacterial culture, *Mycobacterium tuberculosis* DNA testing by polymerase chain reaction, bacterial culture and cytologic analysis were all negative. Cell counting of BAL fluid exhibited lymphocytosis (42.6%), eosinophilia (6.4%) and the study of lymphocyte subpopulations revealed a normal CD4/CD8 ratio (2.2). The abdominal and pelvic ultrasound were unremarkable.

Review of the clinical history in view of this persistent rash revealed that the patient had a previous use of an antibiotic (metronidazole) due to a dental abscess. After 3 days, there was almost complete clinical and analytical resolution.

Given the recent use of a new drug and a new erythematous rash associated with eosinophilia and liver and lung damage without evidence of an eventual autoimmune or an infectious cause, the diagnosis of DRESS Syndrome was made. The patient was discharged and referred to the internal medicine consultation for regular follow-up.

^a Department of Internal Medicine, Centro Hospitalar Tâmega e Sousa - Hospital Padre Américo, Penafiel, ^b Department of Biomedicine, Unit of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Porto, Portugal.

* Corresponding author. Department of Internal Medicine, Centro Hospitalar Tâmega e Sousa - Hospital Padre Américo, Avenida do Hospital Padre Américo 210, 4564-007 Penafiel, Portugal. E-mail address: asgsoares@gmail.com (Sofia Garcês Soares).

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Figure 1. Generalized erythematous rash.

Discussion

We report a case of a 66-year-old male whose complaints of fever, headache and a rash after taking metronidazole led to a broad study showing eosinophilia and liver and lung involvement.

The main causative drugs of DRESS syndrome are allopurinol, anticonvulsants (carbamazepine, phenytoin, lamotrigine), minocycline, sulfasalazine, disulone, fluindione, proton pump inhibitors and strontium ranelate.¹

DRESS syndrome seems to develop in the setting of interaction between genetic and environmental factors, involving reactivation of virus.⁴ Its incidence and whether a racial predilection exist are unknown; there is no age or gender predilection.^{2–4}

Its manifestations are heterogeneous and unpredictable.^{3,5,6} Fever (38–40°C) is the most common sign (90%–100%) followed by skin rash (87%).⁶ Eosinophilia is the most common hematological abnormality (95%), followed by neutrophilia (78%), monocytosis (69%) and atypical lymphocytosis (67%).⁶ Lymphadenopathy has been identified in 54% of patients. The most commonly affected organs are the liver (75%–94%), kidneys (12%–40%), lungs (~30%), heart (4%–27%) and neurological system.⁶

In this particular case, infectious and autoimmune causes were excluded and other causes were unlikely. This patient did not report having previously taken metronidazole, which led to a delay in diagnosis. Nevertheless, metronidazole is not among the drugs most frequently associated to DRESS syndrome. Misdiagnosis is common and the culprit drug may not be identified. Occasionally, patients may present with incomplete or less characteristic features.⁷

The European Registry of Severe Cutaneous Adverse Reactions to Drugs and collection of biological samples (RegiScar) criteria are the most used (Table 1).⁸ The RegiScar scoring for this patient was 6 points so the diagnosis was made: 0 points for the presence of fever, 0 points due to the absence of enlarged lymph nodes in ≥ 2 different areas, 2 points for the presence of ≥ 1500 eosinophils, 0 points due to the absence of atypical lymphocytosis, 1 point for rash ≥ 50 percent of body surface area, 1 point for suggestive rash (widespread infiltrative purpuric lesions on the trunk, abdomen and limbs with facial edema), 2 points for the involvement of 2 organs (liver and lungs), -1 point for rash resolution ≥ 15 days and 1 point for the investigation of an alternative cause.

The main treatment consists of withdrawal of the culprit drug and corticosteroid treatment (which was not necessary in this case) — topical and systemic (prednisone or equivalent: 1 mg/kg/day).¹ According to the expert opinion of the French Society of Dermatology (2010), DRESS syndrome can be managed based on the presence or absence of signs of severity. In the absence of severity signs, the patient can be managed symptomatically with topical corticosteroid emollients and H₁ antihistamines. In the presence of signs of severity (transaminases levels >5 times normal; pneumonia, heart and/or kidney involvement; and hemophagocytosis), treatment includes systemic corticosteroids with a multidisciplinary approach.^{4,6}

Supportive measures, intravenous immunoglobulin therapy, antiviral agents, cyclosporine, mycophenolate mofetil, rituximab and cyclophosphamide have also been described.^{2,3,4,6} Follow-up is crucial because organ involvement may be delayed, flares may occur and manifestations of autoimmunity might develop.^{2,5} The mortality rate is 10% to 40% being hepatic dysfunction the most common cause of death.^{1,6,8}

Table 1**The European Registry of Severe Cutaneous Adverse Reactions to Drugs and collection of biological samples (RegiScar)⁸**

Items	Score			Comments
	1	0	1	
Fever $\geq 38.5^{\circ}\text{C}$	N/U	Y	-	-
Enlarged lymph nodes	-	N/U	Y	> 1 cm and ≥ 2 different areas
Eosinophils $\geq 0.7 \times 10^9/\text{L}$ or $\geq 10\%$ if WBC $< 4.0 \times 10^9/\text{L}$	-	N/U	Y	Score, when $\geq 1.5 \times 10^9/\text{L}$ or $\geq 20\%$ if WBC $< 4.0 \times 10^9/\text{L}$
Atypical lymphocytosis	-	N/U	Y	
Skin rash				Rash suggesting DRESS: ≥ 2 symptoms:
Extent > 50% of BSA		N/U	Y	Purpuric lesions (other than legs), infiltration, facial edema, psoriasiform desquamation
Rash suggesting DRESS	N	U	Y	
Skin biopsy suggesting DRESS	N	Y/U	-	-
Organ involvement	-	N	Y	Score 1 for each organ involvement, maximal score: 2
Rash resolution ≥ 15 days	N/U	Y	-	-
Excluding other causes	-	N/U	Y	Score 1 if 3 tests of the following tests were performed and all were negative: HAV, HBV, HCV, Mycoplasma, Chlamydia, ANA, blood culture

The diagnosis of DRESS Syndrome is based on the total points score—<2: no case; 2–3: possible case; 4–5: probable case; >5: definite case.

ANA = anti-nuclear antibody; BSA = body surface area; HAV=hepatitis A virus; HBV = hepatitis B virus; HCV=hepatitis C virus; N = no; U = unknown; WBC=white blood cell; Y=yes.

There is a lifetime contraindication to use the causal drug and later in the course, skin tests (patch testing is the one recommended) can assist the causality assessment.⁸ On the reassessment, our patient was asymptomatic with no rash recurrence.

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Conflicts of interest

None.

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