

# DRESS: clinicopathological features of 10 cases from an University Hospital in São Paulo\*

## DRESS: características clinicopatológicas em 10 casos de Hospital Universitário em São Paulo

Luciane Francisca Fernandes Botelho<sup>1</sup>  
Maria Helena Valle de Queiroz Padilha<sup>2</sup>  
Adriana Maria Porro<sup>4</sup>

Viviane Shinsato Higashi<sup>1</sup>  
Milvia Maria Simões e Silva Enokihara<sup>3</sup>

**Abstract:** BACKGROUND: Drug reaction with eosinophilia and systemic symptoms is a severe form of drug-induced reaction with multiorgan involvement.

OBJECTIVES: The aim of this study is to evaluate the epidemiological, clinical and pathological features and prognosis of this drug reaction among patients seen at a dermatology service.

METHOD: Retrospective review of medical records of ten patients diagnosed with drug reaction with eosinophilia and systemic symptoms at the Federal University of São Paulo, from august 2008 to may 2011.

RESULTS: Phenytoin was the leading cause of drug reaction with eosinophilia and systemic symptoms in our cases, followed by allopurinol. Abnormal liver function tests were observed in 7 patients and renal function impairment in 2 patients. In all cases, patients were hospitalized and the culprit drug was withdrawn. The main treatment was systemic corticosteroid. Drug reaction with eosinophilia and systemic symptoms resulted in death in 2 cases. The causes of death were septic shock and hepatic failure.

CONCLUSION: Our mortality rate of 20%, supports that drug reaction with eosinophilia and systemic symptoms is a severe form of drug-induced reaction and must be recognized by all dermatologists.

Keywords: Drug eruptions; Drug hypersensitivity; Eosinophilia

**Resumo:** FUNDAMENTOS: A reação a droga com eosinofilia e sintomas sistêmicos é uma reação medicamentosa severa com envolvimento de múltiplos órgãos.

OBJETIVO: Avaliar as características epidemiológicas, clínicas, histológicas e o prognóstico dessa reação medicamentosa entre os pacientes atendidos pelo serviço da dermatologia.

MÉTODOS: Levantamento retrospectivo dos prontuários de dez pacientes diagnosticados com reação a droga com eosinofilia e sintomas sistêmicos pelo serviço de dermatologia da Universidade Federal de São Paulo, entre agosto de 2008 e maio de 2011.

RESULTADOS: A fenitoína foi a principal causa de reação a droga com eosinofilia e sintomas sistêmicos entre os pacientes, seguida pelo alopurinol. A alteração das enzimas hepáticas foi observada em sete pacientes e diminuição da função renal em dois casos. Todos os pacientes estavam hospitalizados e o medicamento implicado foi suspenso. O principal tratamento foi corticóide sistêmico. Dois pacientes faleceram devido à síndrome reação a droga com eosinofilia e sintomas sistêmicos. A causa da morte foi choque séptico e falência hepática.

CONCLUSÃO: A mortalidade de 20% entre os pacientes do estudo confirma que essa reação induzida por droga é grave e deve ser reconhecida por todos os dermatologistas.

Palavras-chave: Eosinofilia; Erupção por droga; Hipersensibilidade a drogas

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<sup>2</sup> Specialist by the SBD (Brazilian Society of Dermatology) - Collaborating physician of the Dermatology Department of the Universidade Federal de São Paulo (UNIFESP) – São Paulo (SP), Brazil.

<sup>3</sup> Master by the Universidade Federal de São Paulo (UNIFESP) – Physician at the Dermatology Department of the Universidade Federal de São Paulo (UNIFESP) – São Paulo (SP), Brazil.

<sup>4</sup> PhD by the Universidade Federal de São Paulo (UNIFESP). Dermatopathologist – Dermatology and Pathology Department of the Universidade Federal de São Paulo (UNIFESP) – São Paulo (SP), Brazil.

<sup>1</sup> PhD by the Universidade Federal de São Paulo (UNIFESP) – Assistant professor of the Dermatology Department of the Universidade Federal de São Paulo (UNIFESP) – São Paulo (SP), Brazil.

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## INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe form of drug-induced reaction with multiorgan involvement. It is characterized by fever, rash, hepatic dysfunction, haematological abnormalities and lymphadenopathy. DRESS usually starts 2-6 weeks after the initiation of drug therapy, and the possible persistence or aggravation of symptoms can occur despite the discontinuation of the culprit drug.<sup>1,3</sup>

Recognizing this syndrome is of particular importance, as the mortality rate is up to 10%. 1-3 The syndrome may proceed to Stevens-Johnson syndrome or toxic epidermal necrolysis.<sup>4</sup>

It is still a matter of debate whether reactivation of several herpes viruses in the course of the disease is part of the syndrome.<sup>1,3</sup>

A total of 44 drugs were described to be associated with DRESS. Of these, the most frequently reported drugs were carbamazepine, allopurinol, sulfasalazine, phenobarbital, lamotrigine, and nevirapine.<sup>1</sup> The aim of this study was to evaluate epidemiological, clinical and pathological features and prognosis of patients with DRESS syndrome of our University Hospital in São Paulo (Brazil).

## MATERIALS AND METHODS

All DRESS patients diagnosed at Federal University of São Paulo, department of dermatology, from august 2008 to may 2011 were included. Demographic characteristics, clinical course, culprit drugs, latency periods, extent of organ involvement, laboratory results, pathological findings, complications and outcome data were collected. Histopathological findings of skin biopsies were also reviewed.

We used the RegiSCAR's scoring system recently published to classify the cases.<sup>5</sup> The scoring system is shown in table 1.<sup>5</sup> Detection of HHV-6 infection was not performed. The study was approved by the Research Ethics Committee of the Federal University of São Paulo.

## RESULTS

There were 10 total cases (6 male and 4 female). The mean age was 45,7 years (range 20-66 years) with a median age of 48 years.

Phenytoin (4 of 10, 40%) was the leading cause of DRESS in our series of cases, followed by allopurinol (2 of 10, 20%), carbamazepine (1 of 10, 10%) and diclofenac (1 case of 10, 10%). In one additional case both carbamazepine and phenytoin were probably implicated. One patient received multiple medications during hospitalization and his diagnosis was

made from medical history, histological examination consistent with drug reaction and other tests negative for bacteremia and hepatitis.

In seven cases, information concerning the time period from using the culprit drug to onset of DRESS were available and ranged from 2 to 6 weeks.

The cutaneous eruption was described as a maculopapular rash or a generalized exanthematous rash in all patients. One patient had also oral mucosa involvement.

A history of fever (> 38°C) was seen in 7 patients (70%); 2 patients had lymphadenopathy (20%) and 4 patients had facial edema (40%).

Abnormal liver function tests were observed in 7 patients and renal function impairment in 2 patients. No patient had involvement of the pancreas and heart.

Haematological abnormalities included leukocytosis (> 10 000/mL) in all patients, eosinophilia (> 1500/mL) in 9 patients (90%), and atypical lymphocytes in one patient (10%).

Skin biopsies were performed in nine patients. Interface dermatitis was observed in 6 patients. Three skin biopsy specimens showed vasculitis. The perivascular inflammation was infiltrated by mixed cells in four patient and eosinophils in two patients. We tried to correlate histological findings with the drug involved, but it was not possible. Different drugs have determined similar histological manifestations, as well as reactions caused by the same drug also exhibited distinct findings on biopsy tissue.

According to scoring System for Classifying DRESS six cases were classified as definitive cases and four as probable cases.

In all cases, patients were hospitalized and the culprit drug was withdrawn. The main treatment was systemic corticosteroid (oral prednisone 1mg/kg/day). DRESS syndrome resulted in death in 2 cases. The cause of death was septic shock in patient number 2 and hepatic failure and septic shock in patient number 8. All data from the 10 patients are shown in table 2.

## DISCUSSION

Male accounted for the majority of the cases in this sample. There were 6 males and 4 females. Articles published with a large number of patients showed different results regarding gender predominance.<sup>1,2,6,7</sup> In certain populations males predominate and in others females. The mean age was 45,7 years (ranging from 20-66 years). Previous studies show mean age of 40,7 years and 51 years.<sup>1,2,7</sup>

In this study, phenytoin was the most common culprit drug. Such finding differs from Taiwan studies, but is in accordance with two previous studies from

**TABLE 1:** Scoring System for Classifying DRESS cases as definite, probable, possible, or no case - according Kaurdaun et al, 2007

Score	-1	0	1	2
Fever $\geq 38.5^{\circ}\text{C}$	No/U	Yes		
Enlarged lymph nodes		No/U	Yes	
Eosinophilia		No/U		
Eosinophils			700-1.499/ $\mu\text{L}$	$\geq 1.500/\mu\text{L}$
Eosinophils, if leukocytes $< 4.000/\mu\text{L}$			10%-19.9%	$\geq 20\%$
Atypical lymphocytes		No/U	yes	
Skin involvement				
Skin rash extent (% body surface area)		No/U	$> 50\%$	
Skin rash suggesting DRESS	No	U	yes	
Biopsy suggesting DRESS	No	Yes/U		
Organ involvement*				
Liver		No/U	Yes	
Kidney		No/U	Yes	
Muscle/heart		No/U	Yes	
Pancreas		No/U	Yes	
Other organ		No/U	Yes	
Resolution $\geq 15$ days	No/U	Yes		
Evaluation of other potential causes				
Antinuclear antibody				
Blood culture				
Serology for HAV/HBV/HCV				
Chlamydia/mycoplasma				
If none positive and $\geq 3$ of above negative			Yes	

DRESS = Drug Reaction with Eosinophilia and Systemic Symptom; U = unknown/unclassifiable; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus.

\*After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score  $< 2$ , no case; final score 2-3; possible case; final score 4-5, probable case; final score  $> 5$ , definite case.

Europe.<sup>2,6-8</sup> In Taiwan allopurinol was the leading cause of DRESS and in Europe phenytoin and carbamazepine were mostly involved.<sup>2,6-8</sup> In Brazil previously reported cases of DRESS were due to anticonvulsants.<sup>9,10</sup>

Seven cases of DRESS syndrome were reported with clinical features appearing 2-6 weeks after administration of the suspected drug. This corresponds to the latency period commonly reported in the literature.<sup>1,6,8,11</sup>

Fever was seen in 7 patient (70%) and this result was similar to others that reported fever in 72-87% of patients.<sup>2,7</sup> We observed two patients with lymphadenopathy, which is one of the criteria for diagnosis.<sup>5</sup> Four patients had facial edema and this finding is common among patients diagnosed with DRESS syndrome. However, such symptom is not part of any diagnostic criteria.<sup>5</sup> The liver was the most frequently involved internal organ and others studies showed similar results.<sup>1,2,7</sup>

All patients had leukocytosis ( $> 10\,000/\text{mL}$ ) and 9 (90%) had eosinophilia. This percentage was higher than previously reported.<sup>2,6,7</sup> Two patients had atypical

lymphocytes and one of them had atypical lymphocytes without eosinophilia. According to diagnostic criteria eosinophilia is not a constant finding and the acronym DRESS is questioned as eosinophilia does not necessarily need to be present in this syndrome.<sup>5</sup>

Histological findings were similar to those reported in other studies that showed interface dermatitis in most patients who underwent skin biopsy.<sup>2,7</sup> Two patients had leukocytoclastic vasculitis and two patients presented with infiltration of eosinophils, such findings were also reported in a previous study from Taiwan.<sup>2</sup> We could not establish a correlation between the drug and histological features, but maybe it might be possible with larger number of patients.

Our therapeutic approach consisted on withdrawal of the suspected drug and administration of systemic corticosteroids and one patient received also antihistamine. Such approach is consistent with published studies.<sup>1,2,3,6,7,11</sup>

During hospitalization systemic corticosteroids was gradually tapered and hematologic and biochemical tests were performed. One patient had recurrence

TABLE 2: Epidemiological, clinical and pathological data of DRESS patients

Patient N.	Gender/ Age (years)	Culprit drugs	Latency period (weeks)	Cutaneous eruption	systemic involvement and other findings	WBC ( $\mu$ L) / eosinophil %	Skin rash (biopsy)	Scoring System for Classifying DRESS	Treatment	outcome
1	M/26	carbamazepine	6	generalized maculopapular rash	Fever, liver	33.700/24,1	Interface dermatitis, perivascular infiltrates of mixed cells	6	systemic corticosteroid	relapse
2	M/66	diclofenac	NA	desquamative erythroderma	Liver	13.000/24,9	Spongiotic dermatitis with eosinophils and focal interface dermatitis	5	systemic corticosteroid	died
3	F/20	phenytoin	3	generalized exanthematous rash	Fever	24.300/16	dermal infiltrates of mixed cells and oedema	5	systemic corticosteroid	recovery
4	M/59	Phenytoin/ carbamazepine	NA	disseminated maculopapular rash	Fever, facial edema	16.400/28	Leukocytoclastic vasculitis with eosinophils	6	systemic corticosteroid	recovery
5	F/52	phenytoin	4	disseminated maculopapular exanthema	Lymphadenopathy, facial edema	21.000/39	Leukocytoclastic vasculitis	5	systemic corticosteroid	recovery
6	F/38	allopurinol	3	maculopapular rash on trunk and limbs	Fever, facial edema, liver	65.300/28, atypical lymphocytes	Interface dermatitis, perivascular infiltrates of mixed cells	6	systemic corticosteroid	recovery
7	F/62	phenytoin	4	generalized exanthematous rash	Fever, facial edema, liver	12.900/21	Interface dermatitis and superficial vasculitis	6	systemic corticosteroid	recovery
8	M/26	phenytoin	2	Generalized exanthematous rash, oral mucosa involvement	Fever, facial edema, liver, kidney	32.400/17	Dense dermal infiltrate of mixed inflammatory cells and oedema	8	systemic corticosteroid	died
9	M/64	allopurinol	3	Disseminated maculopapular exanthema	Lymphadenopathy, liver, kidney	12.200/33	Dyskeratotic cells, spongiosis, exocytosis, vacuolar changes of the basal cells, mononuclear cells at the interface and around dermal vessels	5	systemic corticosteroid	recovery
10	M/44	>4 drugs suspected	NA	generalized purpuric maculopapular rash	Fever, liver	40.600/0, atypical lymphocytes	NA	6	Systemic corticosteroid	recovery

NA: not available.

of the syndrome and according to others studies relapse of the condition is often seen.<sup>1,6,8</sup>

In our study, 2 patients died, an overall mortality rate of 20%. The cause of death was septic shock in patient number 2 and hepatic failure and septic shock in patient number 8. In both cases the implicated drugs were suspended early. Previous studies revealed the same causes of death, but our mortality rate was higher than the reported in Europe and Taiwan.<sup>1,2,7</sup>

## CONCLUSION

We studied 10 patients with DRESS, regarding epidemiological, clinical, laboratorial and histological aspects. The drugs mostly implicated were anticonvulsants. Our mortality rate was 20%, supporting that DRESS is a severe form of drug-induced reaction and must be recognized by all dermatologists. □

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### MAILING ADDRESS:

*Luciane Francisca Fernandes Botelho*  
*Rua Borges Lagoa, 508*  
*04038-001 São Paulo, SP*  
*E-mail: lucianebotelho@hotmail.com*

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