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

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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 In all cases, patients were hospitalized and the culprit drug was withdrawn.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, clinicas, 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 allopurinol. 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 corticoide 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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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, hematological 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.\(^1\)\(^5\)

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.\(^1\)

It is still a matter of debate whether reactivation of several herpes viruses in the course of the disease is part of the syndrome.\(^1\)\(^5\)

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.\(^1\)

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.\(^5\) The scoring system is shown in table 1.\(^5\) 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 (4/10, 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 mucous membrane 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.\(^1\)\(^2\)\(^5\)\(^7\)

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.\(^1\)\(^2\)\(^7\)

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

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

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.\textsuperscript{1,6,8,11}

Fever was seen in 7 patients (70%) and this result was similar to others that reported fever in 72-87% of patients.\textsuperscript{2,7} We observed two patients with lymphadenopathy, which is one of the criteria for diagnosis.\textsuperscript{7} 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.\textsuperscript{7} The liver was the most frequently involved internal organ and others studies showed similar results.\textsuperscript{1,2,7}

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

Histological findings were similar to those reported in other studies that showed interface dermatitis in most patients who underwent skin biopsy.\textsuperscript{2,7} 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.\textsuperscript{1,2,3,5,6,7,11}

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

<table>
<thead>
<tr>
<th>Score</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥38.5°C</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarged lymph nodes</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>No/U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils, if leukocytes &lt; 4 000/μL</td>
<td></td>
<td>700-1 499/μL</td>
<td>≥ 1 500/μL</td>
<td></td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>No/U</td>
<td></td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Skin involvement</td>
<td></td>
<td>No/U</td>
<td>&gt; 50%</td>
<td></td>
</tr>
<tr>
<td>Skin rash extent (% body surface area)</td>
<td></td>
<td>No/U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash suggesting DRESS</td>
<td>No</td>
<td>U</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Biopsy suggesting DRESS</td>
<td>No</td>
<td>Yes/U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ involvement*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle/heart</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other organ</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution ≥15 days</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation of other potential causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood culture</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Serology for HAV/HBV/HCV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia/mycoplasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If none positive and ≥3 of above negative</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

NA: not available.
of the syndrome and according to others studies relapse of the condition is often seen.\textsuperscript{1,6,8}

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.\textsuperscript{1,2,7}

\section*{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. \textbullet

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