Prevalencia del síndrome DRESS

RESUMEN
El síndrome DRESS (exantema inducido por fármacos con eosinofilia y síntomas sistémicos) es una reacción idiosincrática (tipo B), que se distingue por eosinofilia periférica y síntomas sistémicos, como fiebre, exantema, linfadenopatía, hepatitis, linfocitos atípicos y elevación de enzimas hepáticas al menos dos veces su valor normal o incremento de la alanina aminotransferasa (ALT) >100 U/L. La incidencia es de 1 por cada 1,000 a 10,000 exposiciones y su mortalidad es de 10 a 20%. El tratamiento se basa en esteroides y en la suspensión del fármaco sospechado. Se comunican los casos de seis pacientes con síndrome DRESS atendidos en el Centro Médico Nacional Siglo XXI, de septiembre de 2012 a septiembre de 2013, que correspondieron a 12.5% de los pacientes atendidos con reacciones adversas a fármacos.

Palabras clave: síndrome DRESS, reacción por fármacos, exantema, eosinofilia, síntomas sistémicos.

Prevalence of DRESS Syndrome

ABSTRACT
DRESS syndrome (Drug rash with Eosinophilia and Systemic Symptoms) is an idiosyncratic reaction (type B), characterized by peripheral eosinophilia and systemic symptoms, such as fever, rash, lymphadenopathy, hepatitis, atypical lymphocytes and elevation of liver enzymes at least twice its normal level or increase of alanine amino transferase (ALT) >100 U/L. Its incidence is of 1/1,000 to 10,000 exposures and its mortality is of 10%-20%. Treatment is based on steroids and on the suspension of the suspect drug. This paper reports the cases of six patients with DRESS syndrome attended at Centro Medico Nacional Siglo XXI, Mexico City, from September 2012 to September 2013, which accounted for 12.5% of patients attended with adverse reactions to drugs.

Key words: DRESS syndrome, drug-reactions, exantema, eosinophilia, systemic symptoms.

Received: August 2013
Accepted: October 2013

Correspondence
Dra. Eunice Giselle López Rocha
Avenida Cuauhtémoc 330
06720 México, DF
aeri_05@hotmail.com

This article must be quoted
DRESS syndrome (Drug rash with Eosinophilia and Systemic Symptoms) is an idiosyncratic reaction (type B), characterized by peripheral eosinophilia and systemic symptoms, such as fever, rash, lymphadenopathy, hepatitis, atypical lymphocytes and elevation of liver enzymes at least twice its normal level or increase of alanine amino transferase (ALT) >100 U/L.1-3

In 1996 Bocquet described patients with exanthema, hematologic alterations, systemic compromise, lymphadenopathy, hepatitis, pneumonia, carditis and nephritis; and proposed diagnostic criteria and the acronym DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) to describe this pathology.4-5

The incidence of DRESS syndrome is 1:1,000-10,000 expositions, it is more common in adults without gender preference, and its mortality is reported in 10-20%, associated mainly with fulminant hepatitis.5-7

There have been some hypothesis proposed to explain its etiology: Figure 1.

1) Epoxide hydrolase enzyme deficiency or alterations. Aromatic anticonvulsivants are metabolized by the cytochrome P450 (CYP-450) system to arene oxide metabolites, which are normally detoxified by epoxide hydrolase or glutathione transferase. Genetic mutations involving epoxide hydrolase result in accumulation of toxic metabolites, which can affect function and immunologic responses.6,7 Individuals with alterations in the detoxification system are at increased risk for DRESS/DIHS.7

Clinicians must evaluate pharmacologic interactions, co-administration of lamotrigine and valproic acid, which increases the risk of DRESS syndrome, probably due to the sharing of the glucuronidation pathway.8-9

2) Sequential reactivation of herpes virus: During the course of DRESS/DIHS syndrome reactivation of HHV-6, HHV-7, Epstein-Barr virus and cytomegalovirus can occur, represented as increase in IgG anti-HHV-6 titers and its DNA levels in the second or third week after the onset of the rash. In Japan, HHV-6 reactivation is considered a diagnostic criteria for DRESS/DISH syndrome.9,10 Through the clinical course of DRESS/DIHS, blood samples are negative for viral DNA.10-11

Viral reactivation generates a “danger signal” that stimulates clonal expansion of nonspecific T cells, CD8+ and CD4+ and triggers the deve-
lopment of DRESS syndrome. HHV-6 virus can be integrated into the host DNA that can lead to its congenital transmission.11-13

It is suggested a close relationship between HHV-6 reactivation and the development of DRESS/DISH, as with others herpes virus such as HHV-7, Epstein-Barr virus and cytomegalovirus, because they can reactivate during the clinical course of DRESS/DIHS.14

HHV-6 reactivation induces an increase in IgG anti-HHV-6 titers and its DNA levels during the second or third week after the onset of the rash.

3) Ethnic predisposition. There is a predisposition associated with some ethnicities; in Chinese population HLA-B*5801 is a genetic marker for SSJ/NET and DRESS syndrome induced by allopurinol.15-17

4) T cell mediated. In blood and skin biopsies of patients with DRESS syndrome there are specific T cells to drugs such as lamotrigine and carbamazeptene, which suggests a T cell mediated reaction. Type IVc hypersensitivity and CD8+ T cells have also been found as a mechanism in DRESS syndrome induced by drugs such as abacavir.

DRESS syndrome has been associated with exposure to aromatic anticonvulsivants, tricyclic antidepressants, sulfonamide, linezolid, NSAIDs, ACE inhibitors, beta-blockers, allopurinol and gold salts.17-19

At the beginning of the course, patients with DRESS/DIHS present a decrease in serum levels of IgG, IgA, IgM and B lymphocytes, and they return to normal levels within 1 or 2 weeks. Some of the proinflammatory cytokines increase, such as TNF-γ (tumoral necrosis factor gamma) and IL-6, before HHV-6 reactivation.18

Clinical manifestations and diagnosis

Hypersensitivity syndrome is manifested within 3 weeks and 3 months after the initial exposition to the offending drug.

High fever (>38-40°C) and rash are usually the first signs, especially when anticonvulsivants are associated. Fever can persist despite the suspension of the offending drug.8 A morbilliform rash appears in the face, trunk and extremities in 90% of the cases with development of eritrodermia in some of them.

Periorbital edema is present in 25% of patients, with some developing exfoliative dermatitis, cheilitis and tonsillitis.

Bilateral edema and salivary glands infiltration with xerostomy have been reported and suggest paramyxovirus reactivation.1,5,8 Lymphadenopathy is common (70-75% of the cases), and can limit to lymph nodes or become generalized, painful and disappears when the offending drug is suspended. Lymph nodes can present lymphoid hyperplasia with maintenance of normal lymph node architecture, and/or a pseudolymphomatosus architecture due to polymorph infiltrate by atypical cells, plasmatic cells, histiocytes and eosiinphils, with areas of necrosis, edema and mitotic figures, without Reed-Stemberg cells or capsular invasion, simulating a malignant lymphoma.19-20

Cell blood count shows leukocytosis, eosinophilia (in 30% of the cases) and atypical lymphocytes that resemble those found in mononucleosis, which can be misdiagnosed as Epstein-Barr viral infections or hematologic diseases.

Lymphopenia, leukopenia or leukocytosis can be found days after the onset of symptoms. Leukocytosis can reach 50,000/mm³ and eosinophilia 20,000/mm³, the last one associated with pul-
monary infiltrate and can manifest 1-2 weeks after the onset of the syndrome, even when liver enzymes have return to normal levels.

Hemophagocytic syndrome is not common as a DRESS/DIHS manifestation and it appears usually two weeks after the onset of the rash. Occasionally, leukopenia and thrombocytopenia are found, along with increase of LDH. Bone marrow aspirate can show hemophagocytes.21-22

Organic alterations can manifest as myocarditis/myositis, pericarditis, interstitial nephritis, necrotizing granulomatous vasculitis, encephalitis, meningitis, colitis and thyroiditis. These alterations can begin 1-2 weeks after the onset of the rash. In some cases, shock and acute respiratory distress syndrome can develop, with hypotension, fever, hepatitis, acute renal failure, arthritis or arthralgia and myositis.23

Liver is affected in 50-60% of the patients, presence of hepatitis with increase in liver enzymes levels is common, usually without jaundice. When jaundice occurs it has a bad prognosis and hepatic failure increases its mortality. Hepatic biopsy shows lobular necrosis and dense inflammatory infiltrate with lymphocytes and eosinophils or granulomas. Cholestasis and liver necrosis can be present. Active hepatitis B virus infection in these patients is associated with prolongation of liver dysfunction.9,21,24

Renal involvement occurs in 11% of the patients and is usually associated with allopurinol intake, it manifests as an increase in serum creatinine and urea, decreased creatinine clearance and the presence of eosinophils in the urinalysis.9,24

Interstitial pneumonia with eosinophilia is frequent in patients with DRESS syndrome induced by minocycline.25 Myocarditis can manifest at the beginning of the clinical course or even 40 days after the onset, with the patient showing heart failure, chest pain, sudden tachycardia, dyspnea, hypotension and increase in CPK and CPK-MB enzymes, without changes in troponin levels. Echocardiography shows decreased ejection fraction and chest X-ray can show cardiomegaly, with the electrocardiogram showing nonspecific changes in ST-T segment or atrioventricular blockade induced by dapsone.25,26

Neurologic alterations, such as meningitis and encephalitis can develop, also gastrointestinal manifestations with digestive bleeding associated with ulcers secondary to CMV.26

Some reports of autoimmune diseases and/or production of auto-antibodies have been documented, especially in younger people who presented DRESS/DIHS months or years ago. These autoimmune diseases include type 1 diabetes mellitus, lupus erythematosus, Hashimoto thyroiditis, Graves’ disease, thyrotoxicosis, enteropathy, graft versus host disease like lesions, pemphigus, limbic encephalitis, inappropriate anti-diuretic hormone secretion syndrome, spleen rupture, eosinophilic colitis, lethal enterocolitis, eosinophilic esophagitis and myocarditis.20,26-28

HHV-6 reactivation and thrombocytopenia are bad prognosis factors.

Skin biopsy can show dense superficial lymphocytic infiltrates, perivascular affection in papillary dermis; in severe cases they can be present in the epidermis, with edema, eosinophils, atypical lymphocytes, and granulomas, the last ones associated to repeated drug exposition.16,28

Diagnostic criteria of Boquet et al are the most frequently used. Table 1
The Japanese group for the study of severe cutaneous adverse reactions (SCAR-J) suggests that HHV-6 reactivation should be included, as it presents mainly in Japanese population and its detection is not feasible.

The international group RegisCAR, which studies severe cutaneous adverse reactions to drugs, takes into account for the diagnostic criteria biopsy and at least three negative biological investigations that exclude differential diagnosis; however, it does not always justify the cost-benefit of them.11,15

To determine the offending drug associated with DRESS is a challenge. In order to establish the diagnosis we must make an appropriate clinical history and meet Boquet’s criteria. Some authors have suggested the use of patch test. In a series of 56 patients with DRESS induced by anticonvulsivants, they had a positive result in 17 patients (51.5%), and found carbamazepine as the responsible of 13 of the cases, followed by lamotrigine (2 cases), phenytoin (1 case) and topiramate (1 case), showing safety and utility, mainly for anticonvulsivants, because of its specificity.4,28

Positive reactions correspond to a localized inflammatory response, based on specific T cell activation against the drug, serving as cytotoxic effector cells.

Lymphocyte transformation test evaluates specific T cell activation to a certain drug and has a sensibility of 60-70% and a specificity of 85%. It has a better diagnostic value than patch test, and it is recommended 5-8 weeks after the onset of DRESS syndrome. A negative test can not exclude the diagnosis (Figure 1).

### Differential diagnosis

Differential diagnosis includes several conditions such as viral infections, other drug reactions like Stevens-Johnson and toxic epidermal necrolysis; toxic shock syndrome, sepsis, lymphoma,
leukemia, vasculitis, Kawasaki disease, hypereosinophilic syndrome and Still disease.4

**Treatment**

The first step is the early recognition of DRESS syndrome and immediate withdrawal of responsible the drug.2

The use of prednisone or its equivalent at a 1-1.5 mg per kilogram per day reduces the symptoms and improves laboratory alterations, besides the effect of IL-5 on eosinophils. If this treatment is not effective, some authors recommend the use of methylprednisolone (30 mg per kg per day) in pulses for 3 days, immunoglobulin, plasmapheresis or a combination of them. The recommendation is to maintain the systemic steroid dose for 6-8 weeks to avoid relapse, which is usual when the steroid is suspended abruptly.9,14

Immunosuppressive therapies can increase the risk of infections or sepsis.4,19

Clinicians must watch liver and renal function in these patients, as well as specific organ involvement.19

French Dermatology Society classifies DRESS syndrome treatment according to its severity and recommends the use of systemic steroids to 1 mg per kilogram per day or its equivalent in patients with any of the following: increase in liver enzymes five times its normal level, renal involvement, pneumonia, hemophagocytic syndrome or cardiac involvement, for patients with vital risk use of IVlg at a dose of 2 g per kg in 5 days and proposed the use of steroids along with ganciclovir in patients with signs of severity and confirmed HHV-6 reactivation.11,19

In case of fever clinicians can prescribe antipyretics and skin care in order to reduce skin symptoms.11

N-acetylcisteine at high doses is proposed because it is a glutathione precursor, which is a molecule implicated in the detoxification pathway of several drugs and has an immunomodulatory effect by inhibition of inflammatory cytokines and ICAM-1 expression in keratinocytes.11

Other treatments with anecdotal reports used in DRESS treatment are cyclosporine, cyclophosphamide and thalidomide.

The objective of this study was to describe the prevalence of DRESS syndrome in a third level hospital in Mexico City and the cases presented during one year.

**CLINICAL CASES**

At Centro Medico Nacional Siglo XXI (which is a third level reference hospital for the south of México City), we have had 48 patients with adverse drug reaction diagnosis, from September 2012 to September 2013, and 6 of them have met DRESS syndrome criteria, with a prevalence of 12.5%. Here we describe their clinical features and the treatment used in these cases.

**Case 1**

A 46-year-old female, with type 2 diabetes mellitus and diabetic neuropathy, who had 6 weeks history of carbamazepine administration, with an increase in the dose of the last 1 week before the onset of her symptoms. She started her suffering 7 days before her hospital admission, with pruritus, maculopapular exanthema that started in the face, upper trunk and lower extremities, and facial edema (Figure 2). She received a single dose of parenteral steroid and first generation antihistamine H1, showing partial improvement. Three days later she developed cervical lymphadenopathy, right upper quadrant pain and malaise, without fever.
At the first physical examination she had facial edema, disseminated maculopapular exanthema, skin desquamation, painful cervical lymphadenopathy with a 2 cm diameter and liver pain.

Her initial laboratory tests showed AST 40 U/L, ALT 128 U/L, GGT 1319 U/L, LDH 629 U/L, AP 520 U/L, leukocytes 11,700/mm³, neutrophils 2,320/mm³, eosinophils 5,040/mm³, lymphocytes 2,940/mm³, hemoglobin 14.5 g/dL, hematocrit 43%, platelets 349,000/mm³, CPK 26 U, CPK MB 29 U. Atypical lymphocytes were not detected in peripheral blood.

She received treatment with systemic steroid at a dose of 1.5 mg/kg/day (equivalent to prednisone), first and second generation H1 and H2 antihistamines.

At day number 4 of hospital admission she had an increase in eosinophil count, so we decided to increase the prednisone dose to 2 mg/kg/day. With this decision she had a decrease in eosinophil count, with normal levels at her hospital discharge.

Transaminases and GGT levels gradually decreased after the onset of treatment. She had a good progress with peripheral eosinophils and liver enzymes returning to normal levels, so we decided to decrease the prednisone dose to 5 mg/day. Soon after this, the patient had a relapse with exanthema persistence and discrete increase in peripheral eosinophil count. We increased the prednisone dose to 10 mg/day and slowly decrease the dose to its withdrawal.

**Case 2**

A 77-year-old male, with low back pain began treatment with carbamazepine 7 weeks before his hospital admission, with an increase in the dose 1 week before the onset of his symptoms.

He developed skin lesions in scalp and a generalized maculopapular exanthema, fever, and facial edema. At the physical examination he had a morbilliform maculopapular exanthema, facial edema, without lymphadenopathy (Figure 3).

His laboratory tests were AST 33 U/L, ALT 60 U/L, GGT 114 U/L, LDH 502 U/L, AP 89 U/L, leukocytes 8,800/mm³, lymphocytes 1040/mm³, eosinophils 1,760/mm³, with 10% of atypical lymphocytes and negative serology for Epstein-Barr virus and CMV.

We started treatment with systemic steroid at a 1.5 mg/kg/day of prednisone equivalent, and the patient’s peripheral eosinophil count and transaminases levels returned to normal.

**Case 3**

A 22-year-old male with convulsive crisis secondary to traumatic brain injury treated with
phenytoin, began with fever of 39°C 8 weeks after the onset of phenytoin and disseminated maculopapular exanthema that started in the neck. He sought medical attention and was treated as scarlatina with penicillin. During his hospital stay an increase in transaminase levels (twice its normal level) was detected. Fifteen days later he developed headache, hyporeactivity and incoherent speech, so a lumbar puncture was performed, which lead to the diagnosis of aseptic meningitis, tomography and MRI showed no structural alterations. The patient had shown persistent eosinophilia (2,500/mm³), increase in transaminase levels, lymphadenopathy and hepatomegaly so we reached the diagnosis of DRESS syndrome, and we began treatment with systemic steroid (prednisone 1 mg/kg/day) for 6 weeks with a good response. After this we slowly decreased the dose until withdrawal in 4 months.

Case 4

A 48-year-old female with epilepsy treated with carbamazepine for 8 years, she stopped taking her medication in 2009 and switches to oxcarbazepine after she had brain surgery to remove a temporal cyst. She had a convulsive crisis and was treated with phenytoin. Six weeks after she began with phenytoin intake, she presented a maculopapular morbilliform exanthema, facial edema and fever (38.0°C). Her physical examination showed cervical lymphadenopathy (> 1 cm in diameter), hepatomegaly and a morbilliform generalized rash in the trunk and upper limbs as well as facial edema.

Her laboratory tests showed eosinophilia 2,800/mm³, AST 53 U/L, ALT 52 U/L, GGT 225 U/L, LDH 728 U/L, AP 249 U/L, serum creatinine 1.2 mg/dL, 11% peripheral atypical lymphocytes, urinalysis showed 4 erythrocyte per HPF, 10 leukocytes per HPF and eosinophils present in urine; serology for CMV, HHV-1 and HHV-2 was negative. She was treated with systemic steroid equivalent to prednisone 1.5 mg/kg/day.

Case 5

A 44-year-old male with convulsive crisis secondary to a temporal angioma cavernous began treatment with phenytoin and 6 weeks later he developed fever of 38.0°C, maculopapular exanthema and cervical lymphadenopathy. His physical examination showed cervical and behind the ear lymphadenopathy and a generalized morbilliform exanthema.

His laboratory tests showed eosinophils 500/mm³, 30% peripheral atypical lymphocytes, AST 68 U/L, ALT 94 U/L, GGT 911 U/L, AP 139 U/L. Serology for CMV, HHV-1 and HHV-2 was negative.

He began treatment with systemic steroid equivalent to prednisone 1.5 mg/kg/day.

Case 6

A 39-year-old female in treatment with phenytoin after has suffered traumatic brain injury, started with fever 39.5°C, and three days after she began with maculopapular morbilliform exanthema in face, trunk and lower limbs (Figure 4). Her physical examination showed liver pain. Her laboratory test showed eosinophils 1,320/mm³, AST 105 U/L, ALT 107 U/L, GGT 1,180 U/L, AP 421 U/L. We began treatment with systemic steroid equivalent to prednisone 1 mg/kg/day (Table 2).

DISCUSSION

DRESS syndrome is an idiosyncratic hypersensitivity reaction, unrelated to a drug’s dose and associated mainly to aromatic anticonvulsivants.

There is cross reactivity among aromatic anticonvulsivants and they include phenytoin, phenobarbital and carbamazepine, all of these drugs have a similar metabolism, which suggests intermediate metabolites as the responsible for the etiology.
We present 6 cases of DRESS syndrome secondary to aromatic anticonvulsivants, all the patients began with their symptoms 6-8 weeks after the administration of the offending drug; which in 2 cases was carbamazepine, in 4 of them was phenytoin, and in 2 cases there was an increase in the dose before the onset of the symptoms.

These patients showed a morbilliform exanthema, and in 1 case fever was absent. Three patients had facial edema, 5 patients had lymphadenopathy and in none of the cases was mucosal involvement. There are 3 different diagnosis criteria for DRESS syndrome, they differ in HHV-6 detection (which is not available in all hospitals) and the exclusion of other differential diagnosis.

All of the patients had peripheral eosinophilia between 500-5,040/mm$^3$, and only 3 patients had atypical lymphocytes. Even when HHV involvement is important, we only had 1 case of meningoencephalitis, which is very uncommon.

In all cases we immediately suspended the offending drug and started systemic steroid equivalent to prednisone at 1.5-2 mg/kg/day for an average of 15 weeks.

One patient had 2 relapses, one at the begging of the treatment and the other when the steroid dose was decreased, with an increase in peripheral eosinophil count and exanthema, and in both relapses there was a good response to an increase in the steroid dose and a gradual decrease.

All 6 patients had good response to treatment before their hospital discharge, and are actually asymptomatic, without steroids and normal laboratory tests.

### Table 2. Clinical and laboratory characteristics of DRESS syndrome cases

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Offending drug</strong></td>
<td>Carbamazepine</td>
<td>Carbamazepine</td>
<td>Phenytoin</td>
<td>Phenytoin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td><strong>Clinical manifestations</strong></td>
<td>Fever, lymphadenopathy, maculopapular rash, facial edema, anicteric hepatitis</td>
<td>Fever, maculopapular rash, headache, hyporesponsiveness, lymphadenopathy, anicteric hepatitis</td>
<td>Fever, maculopapular rash, facial edema, anicteric hepatitis</td>
<td>Fever, maculopapular rash, lymphadenopathy, anicteric hepatitis</td>
<td>Fever, maculopapular rash, lymphadenopathy, anicteric hepatitis</td>
</tr>
<tr>
<td><strong>Eosinophils in peripheral blood at diagnosis</strong></td>
<td>5,040/mm$^3$</td>
<td>1,760/mm$^3$</td>
<td>2,500/mm$^3$</td>
<td>2,800/mm$^3$</td>
<td>500/mm$^3$</td>
</tr>
<tr>
<td><strong>Atypical lymphocytes</strong></td>
<td>Absent</td>
<td>10%</td>
<td>Absent</td>
<td>11%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
<td>4 months and 2 weeks$^1$</td>
<td>4 months</td>
<td>4 months</td>
<td>4 months</td>
<td>4 months</td>
</tr>
</tbody>
</table>

$^1$ Case 1: patient relapsed during treatment, resolved again increasing steroid dose and gradually decreasing.
CONCLUSION

Early recognition of DRESS syndrome and the associated drug reduces mortality; in order to reduce the risk of relapse clinicians must slowly decrease the steroid dose, always carefully watching the patient’s clinical condition, liver enzymes and peripheral eosinophil count. The duration of treatment is recommended to be at least of 15 weeks.

REFERENCES