Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) / Drug-Induced Hypersensitivity Syndrome (DIHS): a review of current concepts*

Reação a drogas com eosinofilia e sintomas sistêmicos (DRESS) / Síndrome da hipersensibilidade induzida por droga (DIHS): revisão dos conceitos atuais

Paulo Ricardo Criado[1]
Roberta Fachini Jardim Criado[2]
João de Magalhães Avancini[3]
Claudia Giuli Santi[1]

Abstract: The Drug Reaction with Eosinophilia and Systemic Symptoms syndrome, also known as Drug Induced Hypersensitivity Syndrome presents clinically as an extensive mucocutaneous rash, accompanied by fever, lymphadenopathy, hepatitis, hematologic abnormalities with eosinophilia and atypical lymphocytes, and may involve other organs with eosinophilic infiltration, causing damage to several systems, especially to the kidneys, heart, lungs, and pancreas. Recognition of this syndrome is of paramount importance, since the mortality rate is about 10% to 20%, and a specific therapy may be necessary. The pathogenesis is related to specific drugs, especially the aromatic anticonvulsants, altered immune response, sequential reactivation of herpes virus and association with HLA alleles. Early recognition of the syndrome and withdrawal of the offending drug are the most important and essential steps in the treatment of affected patients. Corticosteroids are the basis of the treatment of the syndrome, which may be associated with intravenous immunoglobulin and, in selected cases, Ganciclovir. The article reviews the current concepts involving this important manifestation of adverse drug reaction.
Keywords: Drug eruptions; Drug hypersensitivity; Eosinophilia

Resumo: A síndrome Reação a Drogas com Eosinofilia e Sintomas Sistêmicos, também conhecida como Síndrome da Hipersensibilidade Induzida por Droga apresenta-se clinicamente como uma erupção cutâneo-mucosa extensa tipo exantemática, associada a febre, linfadenopatia, hepatite, anormalidades hematológicas com eosinofilia e linfócitos atípicos, e pode envolver outros órgãos, produzindo insuficiência renal, infiltrado eosinofílico cardíaco e pulmonar, além de pancreatite. O reconhecimento desta síndrome é de suma importância, uma vez que, a taxa de mortalidade é de cerca de 10% a 20% e uma terapia específica pode ser necessária. Sua etiopatogenia está relacionada a drogas específicas, principalmente os anticonvulsivantes aromáticos, alterações imunes, reativação sequencial de herpesvirus e associação com alelos do HLA. O pronto reconhecimento da síndrome e a retirada da droga desencadeante são os passos mais importantes e essenciais no tratamento dos doentes acometidos. Os corticosteróides são as medicações de escolha para o tratamento da síndrome, podendo ser associados imunoglobulina intravenosa e em, alguns casos selecionados, Ganciclovir. O artigo traz uma revisão dos conceitos atuais que envolvem essa importante manifestação de reação adversa a drogas.
Palavras-chave: Eosinofilia; Erupção por droga; Hipersensibilidade

Received on 25.07.2011.
Approved by the Advisory Board and accepted for publication on 04.10.2011.
* Work performed at the Hospital das Clínicas of the Faculdade de Medicina of the Universidade de São Paulo (FMUSP) – São Paulo (SP), Brazil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial Support: None / *Suporte financeiro: nenhum*

[1] PhD in Sciences (Dermatology) by the Faculdade de Medicina of the Universidade de São Paulo (FMUSP) – Dermatologist at the Dermatology Division of the Hospital das Clínicas of the Faculdade de Medicina of the Universidade de São Paulo (FMUSP) – São Paulo (SP), Brazil.
[2] Master in Medicine by the Instituto de Assistência Médica ao Servidor Público Estadual (IAMSPE) – Teaching Assistant of Dermatological Allergy, from the Discipline of Dermatology of the Faculdade de Medicina do ABC (FMABC) – Santo André (SP), Brazil.
[3] Graduated Physician by the Faculdade de Medicina of the Universidade de São Paulo (FMUSP) – Resident Physician of the Hospital das Clínicas of the Faculdade de Medicina of the Universidade de São Paulo (FMUSP) – São Paulo (SP), Brazil.

DEFINITION

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome formed by the acronym derived from the term "Drug Rash with Eosinophilia and Systemic Symptoms", coined by Bocquet et al, also known as Drug-Induced Hypersensitivity Syndrome (DIHS), was first recognized in 1950 by Chaiken, in a patient using anticonvulsant. [1,2] There are many synonyms used, most of them referring to the origin of the drugs involved in the drug reaction, such as dapsone syndrome, allopurinol hypersensitivity syndrome or the anticonvulsant hypersensitivity syndrome. Although a dermatosis is usual in DRESS, the extent of skin involvement is variable and therefore the 'R' in DRESS was subsequently changed from 'rash' to 'reaction'. [3]

Clinically, in its complete form, this syndrome includes an extensive mucocutaneous rash, fever, lymphadenopathy, hepatitis, hematologic abnormalities with eosinophilia and atypical lymphocytes, and may involve other organs with eosinophilic infiltration, producing damage to several systems, especially the kidneys, heart, lungs, and pancreas. [4] This multivisceral involvement differentiates DRESS from other common skin reactions to drugs. Another unique feature of this syndrome is its late onset in relation to the period of introduction of the causative drug, which occurs around 3 weeks to 3 months, and their possible persistence or worsening despite the withdrawal of the offending drug. [2,5]

INCIDENCE

The incidence of this syndrome is estimated to vary from one case among 1,000 to 10,000 drug exposures. [5,6] Adults are more affected than children, and although the precise incidence of the drug reaction has not yet been determined, it is much more common than Stevens-Johnson syndrome (SJS), which has an incidence of 1.2 to 6 cases per million persons-year and most cases are sporadic, with no gender predilection. Recognition of this syndrome is of paramount importance, since the mortality rate is about 10% to 20% and a specific therapy may be necessary. [4]

ETIOPATHOGENESIS

The exact mechanism of DRESS/DIHS remains to be determined but, in cases related to anticonvulsants drugs, three components are considered: (i) deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic amine anticonvulsants (metabolic pathway); (ii) associated sequential reactivation of herpesvirus family; and (iii) ethnic predisposition with certain human leukocyte antigen (HLA) alleles (immune response). [7]

Drugs involved and metabolism:

This type of reaction is most commonly seen with the use of seven different drug groups: (i) anticonvulsants, such as the aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital and primidone), mexiletine, lamotrigine, valproate, ethosuximide, zonisamide; (ii) antidepressants (desipramine, amitriptyline, fluoxetine); (iii) sulfonamides and sulfones (dapsone, sulfasalazine, trimethoprim-sulfamethoxazole, salozosulphopyridine); (iv) anti-inflammatory drugs (piroxicam, naproxen, diclofenac, sundilac, phenylbutazone, ibuprofen); (v) anti-infectives (abacavir, cidofovir, terbinafine, nevirapine , minocycline, linezolid, doxycycline, telaprevir, nitrofurantoin, zalcitabine, spiramycin, metronidazole, piperacillin-tazobactam, ceftriaxone); (vi) angiotensin-converting enzyme inhibitors (captopril, enalapril); (vii) beta-blockers (atenolol, celiprolol). Cases have been reported with allopurinol, gold salts, thalidomide, calcium channel blockers (diltiazem), ranitidine, sorbinil, azathioprine, dobutamine, methimazole, propylthiouracil and efalizumab. [8]

The cases that were more consistent with DRESS/DIHS were caused by aromatic anticonvulsants, dapsone, salozosulphopyridine, allopurinol and minocycline. Other drugs causing less typical cases are reported in the literature, but less frequently. [9] Aromatic anticonvulsants have an estimated occurrence of DRESS/DIHS of one case for every 5,000 people exposed to the drug, and the reaction is especially common among black patients. The aromatic anticonvulsant drugs that have been most frequently associated with DRESS/DIHS are phenytoin, phenobarbital and carbamazepine. However, newer anticonvulsant medications also containing aromatic structure (felbamate, oxcarbazepine, zonisamide and lamotrigine) and the cross-reactivity between the various aromatic anticonvulsant drugs are well documented, varying between 40-80%. Non-aromatic anticonvulsant drugs (topiramate, levitiracetam, tiagabine, ethosuximide, valproic acid and gabapentin) appear to be safe. [8]

Cacoub et al recently reviewed the literature of published cases of DRESS and found 44 drugs related to 172 case reports published in the literature in PubMed/MEDLINE from January 1997 to May 2009 (Table 1). In about one third of cases, the aromatic anticonvulsant drugs were more related to the onset of adverse drug reaction. [10]

Some patients experience a prodrome of flu-like symptoms about 4 weeks before the onset of the clinical reaction. There are reports of DRESS/DIHS even in patients using anticonvulsants for about 40 years. [9]

The pathogenic mechanism of idiosyncratic reactions to drugs, such as DRESS/DIHS has not been

Table 1: Drugs related to DRESS/DIHS

Drug	Cases related to the Drug
Abacavir	5
Allopurinol	19
Amoxicillin plus clavulanic acid	1
Amitriptyline	2
Atorvastatin	1
Aspirin	1
Captopril	1
Carbamazepine	47
Cafadroxil	1
Celecoxib	1
Chlorambucil	1
Clomipramine	1
Clopidrogrel	1
Codein phosphate	1
Cotrimoxazole / Cefixime	1
Cyanamide	1
Dapsone	4
Diaphenylsulfone	1
Efalizumab	1
Esomeprazole	1
Hydroxichloroquine	2
Ibuprofen	2
Imatinib	1
Lamotrigine	10
Mexiletine	5
Minocycline	3
Nevirapine	8
Olanzapine	1
Oxacarbamazepine	3
Phenobarbital	10
Phenylbutazone	1
Phenytoin	7
Quinine and thiamine	1
Salazosulfapirydine	2
Sodium meglumine ioxitalamate	1
Sodium valproate/ethosuximide	1
Spironolactone	1
Streptomycin	1
Strontium ranelate	2
Sulfalazine	10
Sulfamethoxazole	2
Tribenoside	1
Vancomycin	4
Zinosamide	1

Font adapted: Cacoub P et al [10]

fully elucidated. [8] Sullivan and Shear proposed a multifactorial model for the pathogenesis of DRESS/DIHS. [11] Its occurrence would be determined by the combination of exposure to a drug capable of causing adverse reaction given in sufficient dosage and for a certain period of use to a susceptible patient.

A certain group of drugs associated with DRESS/DIHS, including the aromatic anticonvulsants, is metabolized to reactive oxygen intermediates that appear to be inefficiently detoxified in patients with acquired or pharmacogenetic variations of the metabolism of these drugs. [5,8,12]

Aromatic anticonvulsants such as carbamazepine, phenytoin and phenobarbital are metabolized by the hepatic cytochrome P450 (CYP) enzymes and undergo oxidation by aromatic hydroxylation, with subsequent formation of arene oxides. Arene oxides are toxic reactive intermediaries that are normally enzymatically converted to nontoxic metabolites by epoxide hydroxylase or gluthatione transferase. In addition, spontaneous conversion to nontoxic phenol derivatives can occur. In cases of defective or deficiency of epoxyde hydroxylase, arene oxides can accumulate and cause direct cellular toxicity or immune response (Figure 1).

Drug interactions can be important in this syndrome. Concomitant use of lamotrigine and valproic acid increases the occurrence of this syndrome. It is thought that the mechanism for this drug interaction is the competition between valproic acid and lamotrigine for the hepatic metabolism by glucorinidation, which doubles the half-life of lamotrigine and predictably would increase the rate of adverse effects. [7]

Positive patch tests and testing of blast transformation of lymphocytes indicate the presence of an immune reaction in which T cells participate in specific core function. [13,14] Clones of drug-specific T cells have been isolated from patients sensitive to carbamazepine and lamotrigine. [15,16]

Sequential reactivation of herpesvirus in DRESS/DIHS:

Several clinical similarities that could be observed between DRESS/DIHS and infectious mononucleosis (IM) have led to the implication of a possible range of viruses as triggers for this syndrome. In addition, unique features of this syndrome are its late onset in relation to the period of introduction of the causative medication and frequent clinical and laboratory deterioration, and episodes of exacerbation, despite the withdrawal of the offending drug, so that these characteristics are not necessarily typical of a reaction of specific drug etiology. [9]

Although there is a conflicting view on the pathogenesis of DRESS/DIHS in different parts of the world, recent studies have suggested a close relationship between human herpesvirus 6 (HHV-6) and the development of DRESS/DIHS. [17,18]

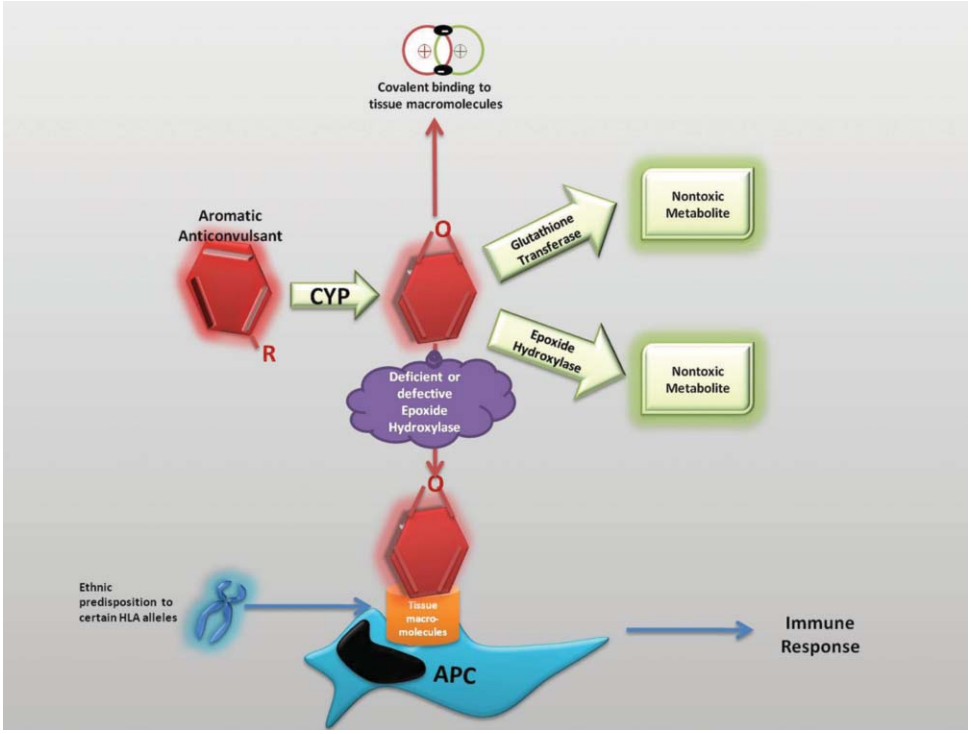

Figure 1: Hypersensitivity to aromatic anticonvulsants. Epoxide hydrolase deficiency leads to reactive oxide arenes accumulation, causing immune response. (CYP= cytocrome P450)

Sporadic reports have shown that not only HHV-6, but also other herpesviruses such as HHV-7, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) can be reactivated during the course of the DRESS/DIHS. [19,20]

Results obtained with the analysis by polymerase chain reaction showed that various herpesviruses are sequentially reactivated during the course of the DRESS/DIHS in most patients. The cascade of viral reactivation is initiated by EBV or HHV-6 and extends over a period to HHV-7 and eventually to CMV. [21] In some patients, the clinical manifestations of this syndrome persist despite discontinuation of the drug involved, coinciding with the reactivation of herpesvirus, as shown in figure 2.

The reactivation of HHV-6 is evidenced by increases in the titles of IgG anti-HHV-6 and their DNA levels. HHV-6 is commonly found in the second or third week after the rash onset, despite the high variability of the clinical manifestations among patients with this drug reaction. [9] Since the reactivation of HHV-6 can be detected only in patients with DRESS/DIHS, but not other adverse drug reaction in Japan, this diagnostic test has become sensitive and specific for diagnosis of all patients with DRESS/DIHS. [17] The detection of HHV-6 reactivation seems to be the gold standard diagnostic test for DRESS/DIHS in Japan, other Asian countries and Europe, helping to confirm the identification of this condition. [9]

However, it is still unknown how the viral genome detection in peripheral blood reflects the true status of viral reactivation in progress in many different organs and systems. That is, it is possible that in different compartments and organs such as the spleen and lymph nodes, different herpes viruses can be reactivated in sequential order completely independent of what occurs in the blood, which would explain why blood samples negative for the viral genome are obtained during the clinical activity of DRESS/DIHS. [9]

What remains unclear is the role of herpesvirus in early DRESS/DIHS. There are two possibilities:

(i) DRESS/DIHS begin as an "allergic" immune reaction to a particular drug, which seems to possess an innate ability to stimulate T cells. [16,22] In the context of T cell activation is a massive activation of herpesvirus housed in these cells, since the stimulation of T cells by the drug may reactivate the viral genome into the cell. So, the drug in turn can activate a specific cellular and humoral immune response to herpesvirus. This could explain why different herpesviruses are activated and because in another intense immune process, the so-called graft-versus-host disease (GVHD), a similar reactivation can be observed. [21]

(ii) The viral reactivation can occur, but is initially clinically unapparent. However, T cells stimulated by virus present a significant cross-reactivity with certain drugs, and exposure to these drugs leads to an expansion of T cells specific to the drug (and viruses),

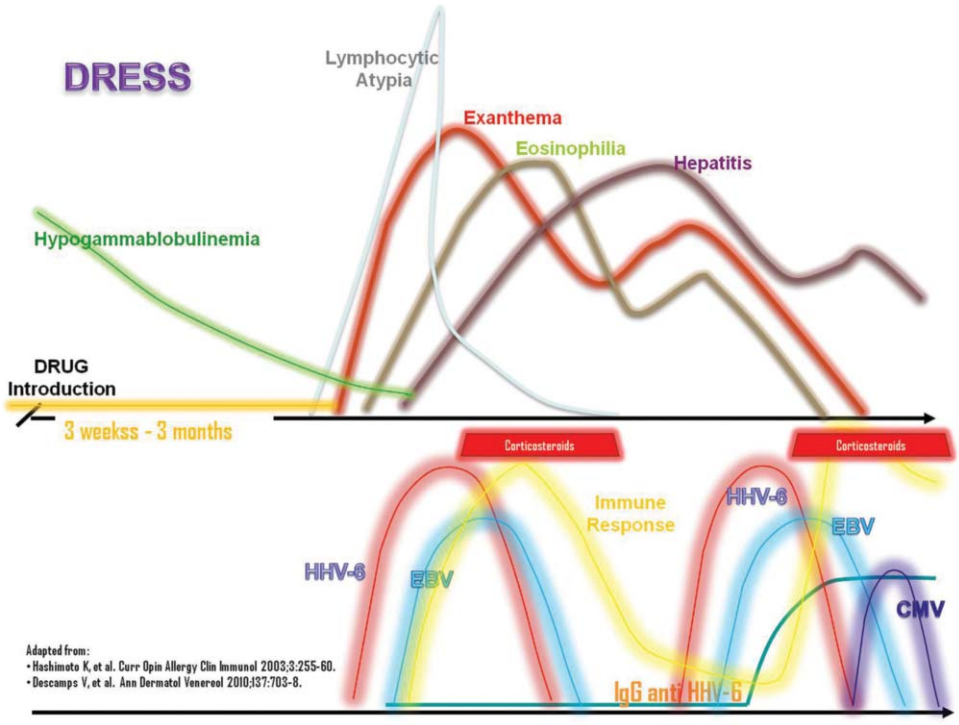

Figure 2: DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms): successive events, since drug exposure, onset of symptoms and viral replication

which persists even after drug withdrawal due the persistence of viral antigens. The simultaneous appearance of multiple concurrent viral reactivations could be explained by the ability of HHV-6 and HHV-7 counterparts to reactivate virus. [23] Thus, if the symptoms of DRESS/DIHS are mediated by both by the various gene products and by the herpesvirus immune responses to viral replication, the frequent deterioration or the several exacerbations that occur despite the offending drug withdrawal, could be, at least in part, from the sequential activation of this herpesvirus.

The viral reactivation may provide a "danger signal" (danger sign) that stimulates massive clonal expansion of both $CD8^+$ and $CD4^+$ non-specific T cells and causes the complete development of the syndrome. [5,11,24] Shiohara et al, proposed the possibility that the clinical symptoms during the course of evolutionary DRESS/DIHS do not seem to be only mediated by oligoclonal expansion of drug-specific T cells, but also by antiviral T cells that cross-react with drugs. [17]

So are all there is necessary for the occurrence of DRESS/DIHS are: i) the drugs; ii) the virus, and iii) their interplay with the immune system. A genetic predisposition has been linked to DRESS/DIHS. [25,26]

How is HHV-6 acquired? HHV-6 infects almost all humans around 2 years of age. [25] Most infections are caused by the exchange of infected saliva during the first year of life, although perinatal transmission can occur. It was demonstrated that the DNA of HHV-6 can be integrated into the host DNA, and once part of the human DNA, congenital transmission can occur. [27] This was also demonstrated in the course of the DRESS/DIHS. [28]

The temporal relationship between the onset of the drug use and the onset of DRESS/DIHS (3 weeks to 3 months) suggests that viruses have no primary function in the syndrome, favoring primary pathogenesis related to drug allergy. [9,25]

Immune aspects involved in DRESS/DIHS

Patients with DRESS/DIHS have decreased total serum IgG, IgA and IgM, and B lymphocyte count at onset while there is an expansion of memory T cells that cross-react with both drug and virus. [24,29] It is noteworthy that the lymphocyte transformation test is negative in the first week of the illness and remains negative in 90% of the patients after two weeks of the onset of symptoms, becoming positive only 5-7 weeks after initiating the drug reaction. [9,25] This could be due to the expansion of regulatory T cells (which suppress the proliferation of memory T cells) in the early stages of the disease and its subsequent reduction by apoptosis. [17]

Several cytokines are increased during DRESS/DIHS. In particular, the levels of TNF-μand IL-6, which are typically pro-inflammatory cytokines, are elevated on this syndrome before the reactivation of HHV-6. [30] Interestingly, IL-6 becomes undetectable during viral replication and increases again after the infection in most patients. [30]

DRESS/DIHS is an entity distinct from other serious adverse drug reactions due to the dynamic changes in the immune response observed during the course of the disease. The phenotype of circulating $CD4^+$ T cells is changed to $CD8^+$ phenotype at the time of viral reactivation. Regulatory T cells are initially increased in number in the circulation and skin, but decrease in parallel with the functional deterioration of the different organs or systems. Figure 3 summarizes the major metabolic changes, immune and viral infections that are interrelated in the pathogenesis of DRESS/DIHS in patients who have the syndrome triggered by aromatic anticonvulsants.

The reactivation of HHV-6 is considered a condition requiring immune suppression, demonstrated on several immune abnormalities in the early syndrome: marked decrease of serum immunoglobulins, the number of circulating B cells and regulatory T cells dysfunction. [24,31,32] The decrease of IgG, IgA and IgM is observed at the beginning and the lowest levels are usually detected several days or a week after withdrawal of the triggering drug. After the immunoglobulin nadir, the recovery to normal levels can be observed within 1 to 2 weeks after the start of the reaction and normal levels are usually achieved during the recovery of the disease. [9,17,24]

Moreover, the participation of skin inflammation may be involved in the induction of immunosuppressive conditions. [31] Sugita et al demonstrated a reduction in the number of plasmacytoid dendritic cells (pDC) in peripheral blood of patients, but an increase in the expression of these cells in the skin affected by the rash. [33] The pDC human leukocyte subtypes are capable of producing large amounts of interferon alpha (IFNα), which induces the maturation of B cells in order to produce IgG and works well with critical role in antiviral defense. [34,35] The pDC from circulation may accumulate in the skin and thus reduce the number of pDC in the circulation. Therefore, antiviral responses may be reduced, facili-

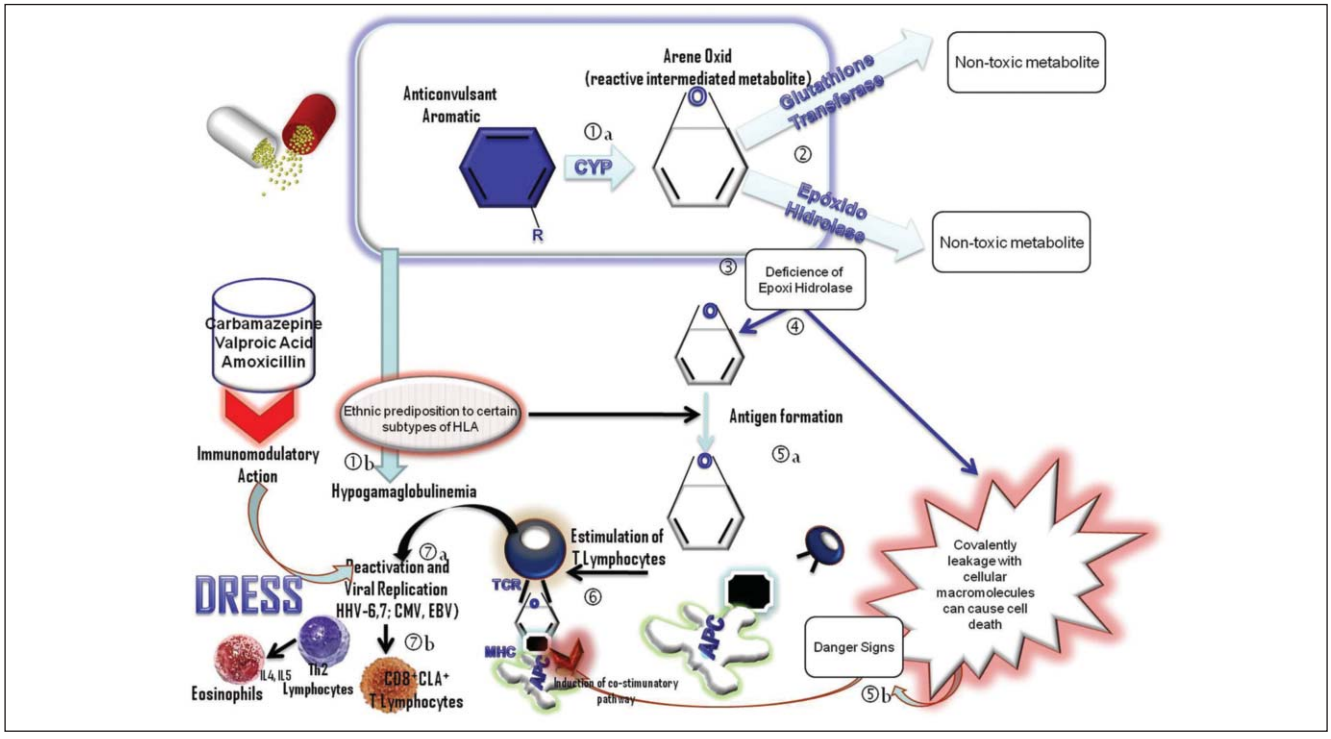

Figure 3: Sequence of events of drug-virus-immune system interaction in patients with DRESS/DIHS triggered by aromatic anticonvulsants. Aromatic anticonvulsants are metabolized by the oxidation system of cytochrome P450 (CYP) in arene oxide radicals (intermediate reactive metabolite) (1a). These arene oxides are detoxified by glutathione transferase and epoxide hydrolase in non-toxic metabolites 2. In genetically predisposed individuals or by additional factors, occurs an impaired detoxification and accumulation of these metabolites 3, which can cause cellular damage generating Danger Signs that can stimulate resting T cells, inducing co-stimulatory pathways 4. In addition, ethnic predisposition to certain HLA types may contribute to the formation of neoantigenes from the combination of these intermediary reactive metabolites with tissue macromolecules and formation of haptens (5a), which can be presented via the human histocompatibility complex class I (HLA -DR) or class II (HLA A, B or C), to CD4 or CD8 T cells 6. It was demonstrated that carbamazepine, valproic acid and amoxicillin are able to exert immunomodulatory actions by inhibiting histone decaboxilase on B lymphocytes, producing a hypogammaglobulinemia that precedes the clinical onset of DRESS/DIHS. The clonal expansion of T cells requires sequential reactivation of latent herpesvirus, and at the same time, CD8 + CLA + T cells are produced, which are directed towards skin, CD8 + CCR4 + T cells addressed to the lungs (7b) and CD4 + IL4, IL5 producer and IL17 CD4Th17 + producer that cause tissue and peripheral eosinophilia

tating viral reactivation in peripheral blood and tissues other than the skin. [31]

Although the terms DRESS and DIHS are often and mistakenly used interchangeably, there is currently a tendency to believe that the DIHS represents the most severe cases of DRESS, with reactivation of HHV-6 detected in a large majority of patients and only in a limited number of patients with DRESS. [31,36]

Associations of HLA alleles with DRESS/DIHS and maculopapular eruption induced by aromatic anticonvulsants or other drugs (pharmacogenomics): The most used hypothesis to explain the immune-allergic reactions to drugs is the theory of hapten / pro-hapten: according to this hypothesis, the drug (or metabolite) is processed by antigen presenting cells (APC) and expressed in the cell membrane in the context of human leukocyte antigen (HLA A, B or C) type I (MHC I) or HLA-D type II (MHCII). The complex HLA-drug (hapten) is presented to native T cells (naive) via their T cell receptor (TCR), which initiates different types of immune responses, depending on the HLA expressed on the APC and the cytokine environment.

The true story of correlation "HLA-drug" began on the twenty-first century with abacavir. In 2002, two independent groups observed the abacavir hypersensitivity syndrome and that this was restricted to the allele HLA-B * 5701, which conferred an elevated odds ratio (> 100). The GlaxoSmithKline (London, UK) led the largest international randomized pharmacogenetic clinical trial to date, which demonstrated the correlation between abacavir hypersensitivity reactions and patients with this allele, and proved that the exclusion of abacavir introduction to the patients that had this allele resulted in the disappearance of the syndrome, which was first seen in 5% of patients overall who received the drug during the first weeks of antiretroviral treatment. This allele test is now routinely used before the introduction of abacavir in several countries.

Some ethnic groups and genetic basis seems to facilitate certain types of adverse drug reactions (Table 2). [37]

The HLA alleles have a high negative predictive value but low positive predictive value in relation to adverse drug reactions, indicating that these biogenetic markers are necessary but not sufficient to trigger the allergic immune reactions. According to the theory of HLA-drug (hapten), the complex hapten only triggers an immune-allergic reaction in the presence of a specific HLA allele.

Thus, prospective HLA screening should prevent some patients from having serious idiosyncratic reactions, such as DRESS/DIHS, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) if they have a specific risk allele by not receiving the drug related to it. The HLA pharmacogenomics is a field of recent study that has been rapidly developed and implemented into clinical practice and has improved drug prescription, which is likely to become more and more important in coming years.

Besides causing SJS and TEN, carbamazepine also induces other types of adverse drug reactions, including maculopapular exanthema (MPE) and DRESS/DIHS. [38] The association between HLA-B*1502 and carbamazepine MPE-induced was not detected in populations of ethnic Han Chinese and Hong Kong or Thai populations. [39,40,41] Studies involving 18 patients Han Chinese residents in Taiwan and 56 Caucasians showed no association between cases of DRESS/DIHS caused by carbamazepine and HLA-B*1502. [42] These data indicate that the association between HLA-B*1502 and cutaneous adverse drug reactions induced by carbamazepine are specific to SJS/TEN. [38]

Kano et al showed that 4 of their 13 Japanese patients (30.8%) with DRESS/DIHS in which it was proved reactivation of HHV-6 and the syndrome was triggered by aromatic anticonvulsants (carbamazepine 10; phenobarbital in 2 and phenytoin in 1) had HLA-B*1301. [43] The frequency of this allele was much higher than the Japanese population in which it is 1.3%. [44] Although this difference was not statistically significant after correction for multiple comparisons, the authors proposed that the presence of certain alleles of HLA-B on the reactivation of the virus contributed, at least in part, for the association of HLA-B allele with DRESS/DIHS.

Kashiwagi et al demonstrated a significant association between adverse skin reactions to carbamazepine and HLA-A* 3101 among 22 Japanese patients, including erythema multiforme, erythroderma, DRESS/DIHS, SSJ and other drug reactions. [45] Eleven of these patients (50%), including 2 patients with SJS and others, were carriers of HLA-A*3101 and allele frequency was much higher in the patients (25%) than in the Japanese population (7.1%) (P = 4x10-4, OR = 4.33).

Hung et al studied 18 patients Han Chinese with MPE induced by carbamazepine and also found an association with HLA-A * 3101 (P = 2.2 x10; OR = 17.5). [41] The sample size of those studies was small, so further studies with larger population samples may or may not clarify the association of HLA-A*3101 allele as a risk for adverse drug reactions.

In a case-control study in a Han-Chinese population, Hung et al found a strong association between the presence of HLA-B*5801 and SJS / TEN, or DRESS/DIHS triggered by allopurinol among 51 patients (100%), compared with 20 out of 135 (15%) allopurinol-tolerant patients and 19 out of 93 control people (20%) (P <6.10, OR = 580). [46]

Table 2: Ethnic groups and genetic basis related to adverse drug reactions

Drug (population)	SJS/TEN	DRESS	MPE	Reference
Carbamazepine (Han Chinese-Taiwan	HLA-B*1502 (Pc 3,1x 10^{-27} a 1,6x10^{-41}; OR 1,37-2,504)	rs 2894342 motilin gene (Pc 0,0064; OR 7,1)	HLA-A*3101 (Pc 2,2x10^{-3}; OR 17,5)	•Nature 2004;428:486. •Pharmacogenet Genomics 2006;16:297-306.
Carbamazepine (Caucasian Europeans)	Weak association with B44. No association with HLA-B * 1502	Haplotypes TNF-308-DR3-DQ2 (Pc 0,02; OR 3,2)	Unknown	•Neurology 2001;56:890-6. •Pharmacogenomics J 2006;6:265-8. •Pharmacogenomics 2006;7:813-8.
Carbamazepine (Southeast Asia)	HLA-B*1502	Unknown	Unknown	•Pharmacogenomics J 2006;6:265-8.
Allopurinol (Han Chinese-Taiwan and Caucasian Europeans)	Chinese: HLA-B*5801 (Pc 4,7x10^{-24} OR 580,3) Europeans: HLA-B* 5801 (P10^{-6} OR 80)		Unknown	•Proc Natl Acad Sci USA 2005;102:4134-9. •Pharmacogenet Genomics 2008; 18:99-107.
Allopurinol (Han Chinese-Singapure)	HLA-B17/BW58 (Pc 2,9x10^{-9} RR 46,3)			•Dermatologica 1989;179:32-33.
Abacavir (Caucasians)		HLA-B*5701 (Pc 5,2x10^{-20} OR 960)		•Proc Natl Acad Sci USA 2004;101:4180-5.
Abacavir (Hispanic or Africans)		No association with HLA-B*5701		•Pharmacogenomics 2004;5:203-11.
Nevirapine		HLA-DRB1*0101 (Australia)	HLA-B*3505 in Thai (P=0.00017; OR 49,15)	•AIDS 2005;19:97-9. •Pharmacogenet Genomics 2010;19:139-42.

Dainichi et al showed that Japanese patients with different clinical types of cutaneous adverse drug reactions caused by allopurinol, including SJS, TEN and DRESS/DIHS, had the same allele HLA-B*5801. [47]

Pirmohamed et al found an increased frequency of HLA-DR3 and HLA-DQ2 in a group of patients with carbamazepine-induced DRESS/DIHS (respectively P = 0.01, OR = 3.3 and P = 0.04, OR = 2.7). [48] It was demonstrated that activation of $CD4^+$ T cells with interleukin-2 (IL-2) is essential for the spread of HHV-6 in vitro. Genotyping of patients revealed that they had positive HLA-DR3 (DRB1*0301) and HLA-DQ2 (DQB1*0201).

Thus, in recent years the attention given to genetic factors as cause to the variation in both the interpersonal effectiveness and adverse effects to medicines has increased. Idiosyncratic reactions are often immune-mediated, usually severe, and have an unpredictable course. The main region of human DNA that has genetic variations that predispose to drug hypersensitivity reactions is the region of the human leukocyte antigen (HLA). This region harbors the gene locus of most diseases and contains many genes associated with immune functions. [49]

Although strong associations have been demonstrated between certain HLA alleles and some types of adverse skin reaction to drugs, there is no definitive evidence or published data concerning the functions involved in these alleles. The activation of T cells restricted to HLA is necessary for the induction of immune reactions and, moreover, there is the possibility that some HLA proteins have high binding affinity with other drugs or a metabolite of the drug through covalent and non-covalent mechanisms. On the other hand, a protective effect of HLA has also been suggested. [38] Alfirevic et al reported a potential protective

effect of HLA-B*0702 against severe adverse skin reactions induced by carbamazepine in Caucasian patients. [42]

The implications of pharmacogenomics are varied, one example is the recommendation by the Food and Drug Administration (FDA), that currently recommends genetic testing for users of more than ten drugs currently marketed in that country. [38]

HISTOPATHOLOGY

Histopathology of the skin shows a diffuse dense lymphocytic infiltrate or superficial and perivascular. Eosinophils in the dermis or swelling may or not be present (Figure 4). On some occasions there is a band-like infiltrate with atypical lymphocytes simulating epidermotropism like mycosis fungoides. [1]

Fernando et al described a patient with DRESS/DIHS triggered by carbamazepine. The biopsy of the rash presented an unusual form of superficial perivascular inflammatory infiltrate, in which tiny granulomas along with a moderate number of lymphocytes could be found. [50] The authors speculated that granuloma formation may be due to a sustained exposure to the drug, even after the onset of DRESS/DIHS.

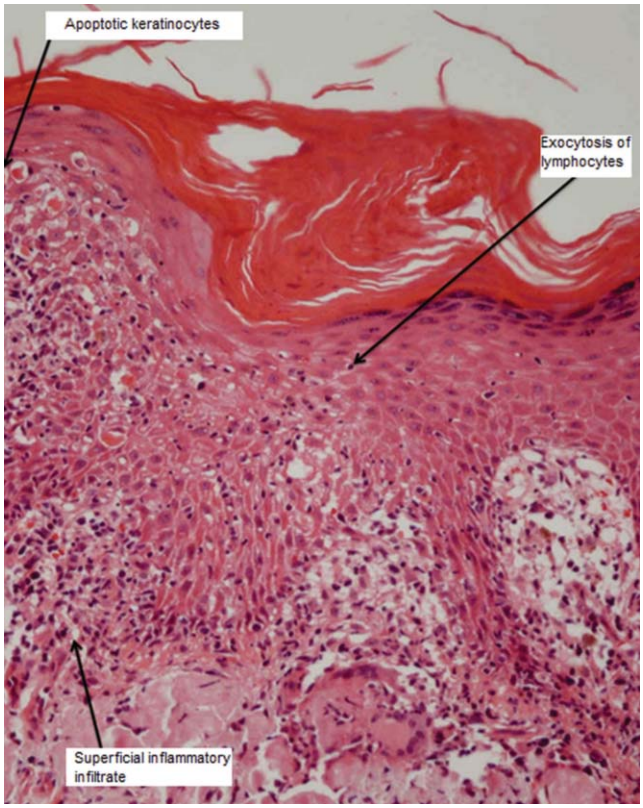

Figure 4: Epidermis showing spongiosis, apoptotic keratinocytes, exocytosis of lymphocytes and inflammatory infiltrate on the superficial dermis. The formation of epithelioid cell granuloma is observed on the superficial dermis, which was sporadically reported in cases of DRESS/DIHS

The expansion of $CD4^+$ T cells producing interferon and other cytokines results in recruitment of macrophages, which as a result of maintained exposure to the drug and persistence of cytokine release, promotes differentiation of macrophages into epithelioid cells, which secrete TNF, which promotes fusion of these cells into multinucleated giant cells.

Thus, biopsies of organs involved in DRESS/DIHS, such as skin and liver, on a significant number of patients may demonstrate the true frequency of granulomatous infiltration in the disease and assist in understanding the pathogenesis of the reaction. [50]

SYMPTOMS AND SIGNS

The syndrome usually develops within two months after drug introduction, more often in 3 weeks to 3 months of the introduction of the drug, or in brief if constitutes a re-administration. [17] Fever, often high (38-40^{O}C), which is the most common symptom (seen in 90-100% of cases) and rash (87% of cases) are the first signs, especially when related to antiepileptic drugs. [25,51-55] The cutaneous eruption consists of a morbilliform rash, which is also common in other less severe drug reactions and both presentations are indistinguishable (Figures 5 and 6). [56]

The face, upper trunk and upper extremities are initially affected, with subsequent progression to the

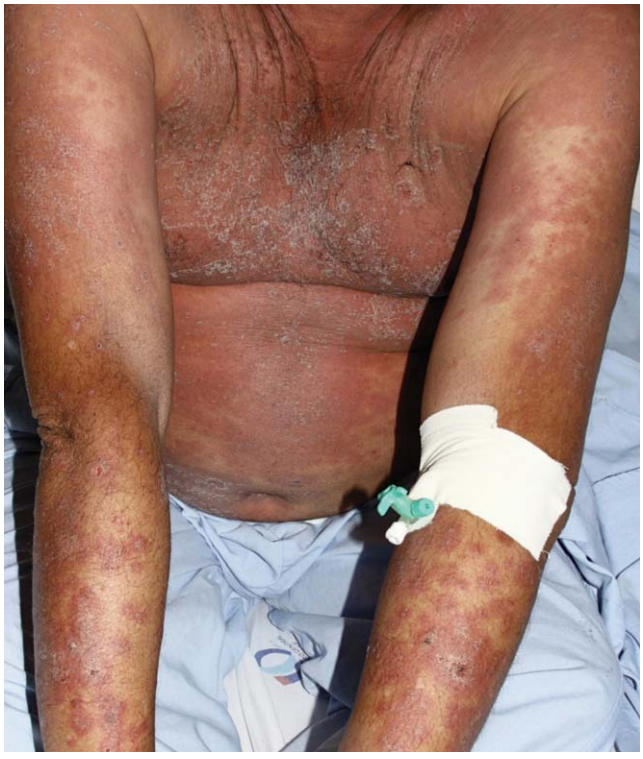

Figure 5: Morbilliform exanthem in a man with DRESS/DIHS caused by the use of anticonvulsants

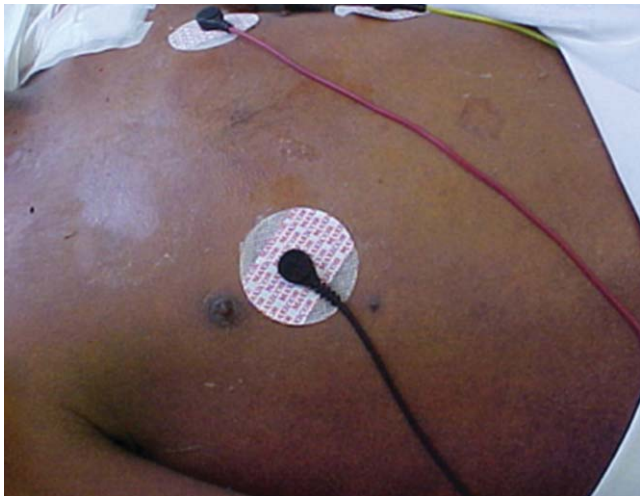

Figure 6: DRESS/DIHS induced by dapsone in a 26 years old patient receiving treatment for Leprosy. The patient died due to hepatic failure

lower extremities, occurring in about 90% of cases, which later spreads to the legs and an erythrodermic rash can be developed. [8]

The maculopapular eruption later becomes infiltrated with edematous follicular accentuation. Swelling of the face, with marked periorbital involvement, is a warning to the diagnosis, occurring in about 25% of patients, and can be so intense that the patient becomes disfigured. Vesicles may arise and fine vesicles by edema of the dermis can be present. [8,54] No necrosis of the epidermis like TEN occurs, except in rare cases of overlapping DRESS/DIHS and TEN. [1,57] Small sterile perifollicular pustules and non-follicular pustules may appear, which are different from acute generalized exanthematous pustulosis, and does not predominate on the main folds of the skin. [53] Often atypical targets may arise. [51,52] Over time the rash becomes purplish, sharply lower limbs and the resolution is scaling. [8,53] Another form of presentation is a picture of exfoliative dermatitis, which may be associated with mucosal involvement, such as cheilitis, erosions, pharygitis and enanthematous enlarged tonsils. [3,58]

Bilateral edema and infiltration of the salivary glands with xerostomia has been frequently reported. [25]

Lymphadenopathy is common (70-75% of cases), limited to the lymph nodes or generalized, painful, gradually resolving with the withdrawal of the drug. [25] The lymph nodes may reveal two distinct types of involvement: a benign pattern of lymphoid hyperplasia with maintenance of normal lymph node architecture, and other standard pseudolymphomatous aspect, with obliteration of normal architecture by a polymorphous infiltrate composed of atypical cells, plasma cells, histiocytes and eosinophils, with areas of necrosis, edema and mitotic figures but no Reed-Sternberg cells or capsular invasion. This histopathological pattern can simulate a malignant lymphoma. [1]

Various hematologic abnormalities are observed, which consist of marked leukocytosis, eosinophilia (30% of cases) and atypical lymphocytes similar to mononucleosis. [1,25] These findings guide the diagnosis toward DRESS, however, can sometimes be difficult to distinguish from viral infections such as infection by Epstein-Barr virus or hematologic diseases. Lymphopenia, leukopenia or leukocytosis usually precede, although they often are not detected because they occur several days before installation of the clinical syndrome. Leukocytosis may be high, up until 50,000 leukocytes/mm^3, and eosinophilia reaches values higher than 20.000/mm^3. [1] The eosinophilia may determine the involvement of internal organs with pulmonary infiltrates. In general, eosinophilia may be observed, about 1 to 2 weeks after the onset of the syndrome, or even occur after the increase in liver enzymes has normalized. [59]

Hemophagocytic syndrome (HPS) can rarely be observed in the course of DRESS/DIHS. HPS is associated with and triggered by various conditions, including viral infections, particularly EBV, malignant tumors, or autoimmune diseases. When in the course of the DRESS/DIHS, HPS usually occurs two weeks after the onset of drug eruption. There is a decrease in white blood cells and platelets that is detected simultaneously with the elevation of lactate dehydrogenase (LDH). Bone marrow aspirate revealed hemophagocytosis figures in an increased number of macrophages. [59]

Multiorgan involvement may include a wide variety of organs and systems with myocarditis/myositis, pericarditis, interstitial nephritis (11% of cases), necrotizing granulomatous vasculitis in kidney, brain involvement (encephalitis or meningitis), colitis and thyroiditis. [1,59] This potentially fatal visceral involvement form, may be symptomatic or not, and initiates 1 to 2 weeks after the onset of a rash. [1,51,52,53,54] We observed a patient who developed acute pancreatitis and has evolved into a lethal course. [51]

There are reports of shock and respiratory distress syndrome with hypotension, pyrexia, hepatitis and renal failure related to a hydantoin reaction. [25]

Arthritis or arthralgia may occur in the context of this syndrome, including myositis [1].

Liver involvement is the most common visceral manifestation (50-60% of patients), after the lymphadenopathy. Hepatomegaly may constitute a finding on physical examination. Hepatitis with isolated elevation of liver transaminases is common (51% of cases), usually anicteric, but liver failure contributes to the leading causes of death [1]. Liver biopsy shows central

lobular necrosis and dense inflammatory infiltrate of lymphocytes and eosinophils or granulomas. [1,59] The reaction is accompanied by cholestasis and hepatocyte necrosis [1]. In more severe cases, widespread or focal hepatic necrosis may be present. [1,60] The presence of an active co-infection with hepatitis viruses B and/or C often determines a deterioration of the liver function and prolongs liver dysfunction. [59,60]

There are few cases reported in the literature of DRESS/DIHS with severe acute hepatitis (defined by the presence of ALT to more 10x ULN and / or acute liver failure, such as coagulopathy and encephalopathy), mostly observed in women between the second and fourth decade of life, especially related to the use of sulfasalazine. [50,59] About 15% result in death or liver transplantation, and the course of the disease is apparently unchanged by the use of immunosuppressant. [50] The fast recognition of the syndrome and prompt withdrawal of the drug can limit the liver damage, although this may possibly even worse for several weeks, and take months to resolve.

Renal involvement occurs in about 11% of cases, being particularly evident in cases arising from the use of allopurinol. [59] There was an increase in serum creatinine and urea and decreased creatinine clearance. In urine I tests, increased content of eosinophils can de observed. [59]

Although pulmonary involvement is rarely reported in DRESS/DIHS, interstitial pneumonia with eosinophilia is often observed among patients who had the syndrome triggered by minocycline. [25] Possibly the cases with lower intensity of pulmonary manifestations are less reported, leading to a bias in the publications. Pulmonary complications include acute interstitial pneumonitis, lymphocytic interstitial pneumonia and adult respiratory distress syndrome (ARDS). [25]

Myocarditis may develop at the beginning of the syndrome or up to 40 days after installation. Symptoms include heart failure, chest pain, sudden tachycardia, dyspnea, and hypotension in early DRESS/DIHS, but some patients are asymptomatic. The echocardiogram shows a reduction in ejection fraction, chest x-ray demonstrates cardiomegaly and the electrocardiogram shows nonspecific changes in the segment ST-T. There is an increase of enzymes such as CPK and CK-MB, but no apparent changes in levels of troponin-1. [59]

Neurological complications include meningitis and encephalitis. Meningoencephalitis occurs about 2 to 4 weeks after onset of the drug reaction, and may determine coma, seizures, headaches and disorders of speech, and paresis and paralysis of cranial nerves. [59]

Gastrointestinal bleeding may be an abrupt complication caused by ulcers caused by CMV. Endoscopic examination reveals arterial bleeding from punched-out gastric ulcerations. [59]

Kennebeck compiled the frequency of clinical manifestations and laboratory data of the anticonvulsant hypersensitivity syndrome: Fever (90-100%), cutaneous eruption (87-90%), limphadenopathy (70%), hepatitis (50-60%), hematological abnormalities (23-50%), periorbital and orofacial edema (25%) , myalgia and arthritis (20%), nefritis (11%), pharyngitis (10%), pulmonary manifestation (9%).[61]

The visceral involvement in acute DRESS/DIHS until resolution of the clinical disease is, therefore, extensive and varied, and some of these events are closely related to human herpervirus reactivation, and include: enterocolitis and intestinal bleeding, hemophagocytic syndrome (HPS), hepatitis, limbic encephalitis, myocarditis, nephritis, mumps, pneumonia and pleurisy, and the *syndrome* of *inappropriate antidiuretic* hormone *hypersecretion* (SIADH). [59]

The exclusion of other serious infections, particularly bacteremia, neoplastic diseases (lymphoma, leukemia, hypereosinophilic syndrome, paraneoplastic), autoimmune or connective tissue conditions (adult-onset Still's disease, lupus erythematosus, vasculitis) is necessary for an accurate diagnosis DRESS/DIHS. [25,62,63]

Complications are rare and include limbic encephalitis, thyroid disease, renal failure, splenic rupture, eosinophilic colitis, eosinophilic esophagitis, enterocolitis and fatal CMV. [64]

Death rate can reach 20%, especially in cases related to advanced age, renal impairment, jaundice and hepatitis with reactivation of CMV. In contrast, cases where there is a reactivation of Epstein-Barr virus (EBV) seems to have less a severe course, but are more likely to have later development (usually after several years) of autoimmune diseases such as diabetes mellitus type 1 and autoimmune hypothyroidism. [25]

Several authors have reported the occurrence of autoimmune diseases and/or the production of autoantibodies after the resolution of DRESS/DIHS, in a period ranging from several months or years after the resolution of the syndrome, and some are similar to those seen after bone marrow transplantation. The related conditions include diabetes mellitus type 1, lupus erythematosus, Hashimoto's thyroiditis, enteropathy, sclerodermiform lesions type graft-versus-host disease (GVHD) and bullous pemphigoid. [59]

DIAGNOSTIC CRITERIA

The diagnosis is difficult since there are incomplete clinical features or less characteristic, for example, hepatitis without rash, or just a pulmonary infiltrate with eosinophilia. Bocquet, Bagot and Roujeau [1] were the first authors who proposed criteria for

DRESS diagnosis. According to these authors the diagnosis is established if there are at least three criteria present: 1. Drug rash; 2. Hematologic abnormalities (a. Eosinophilia > 1.500/mm^3; b. Presence of atypical lymphocytes); 3. Systemic involvement [Adenopathy (> 2 cm in diameter) or hepatitis (transaminase elevation of at least twice the normal values) or interstitial nephritis or pneumonitis or carditis].

There is still no international consensus on the best criteria for the definition of DRESS/DIHS diagnosis. [65] Bocquet et al and Southeimer & Houpt have proposed different definitions and nosology for DRESS/DIHS, in order to clarify clinical and pathological characteristics of this syndrome. [1,66]

The Japanese study group of severe cutaneous adverse reactions to drugs (SCAR-J) has adopted other criteria, as presented on table 3. [17]

However, the universal adoption of these criteria may be impaired, because one of the criteria is the viral replication during the course of infection, and some tests, such as measurement of IgG titer anti-HHV-6 (human herpesvirus type 6), are not yet widely available in all hospitals or laboratories routine.

In our view, the criteria adopted by the European group RegiSCAR is the one that best meets the needs in the diagnosis of DRESS/DIHS, published by Kardaun et al in 2007. It was suggested the use of a score system for the diagnosis of DRESS/DIHS, based on the presence of symptoms and clinical and laboratory signs, which can be seen on table 4. [67]

Table 3: SCAR-J diagnostic criteria for DRESS/DIHS

1. Maculopapular rash developing > 3 weeks after starting therapy with a limited number of drugs
2. Persistent clinical findings after drug withdrawal
3. Fever (> 38°C)
4. Hepatic abnormalities (TGP > 100 U/L)
5. Leukocyte abnormalities (at least one present) a. Leukocytosis (> 11.000/mm3) b. Atypical lymphocytosis (>5%) c. Eosinophilia (>1.500/mm3)
6. HHV-6 reactivation

The diagnosis is confirmed by the presence of the seven criteria (typical DIHS) or of the first five criteria (atypical DIHS).
* This can be replaced by other organ involvement such as renal involvement.
+ Reactivation is detected from second to third week after symptoms onset, through IgG anti-HHV-6 titers elevation.

Complementary tests during follow-up of patients with DRESS/DIHS:

Given the suspicion of the syndrome relevant exams should be performed, keeping in mind that this syndrome has an evolutionary behavior. [63] The initial tests are oriented in order to verify the data and research into hematological visceral involvement, as proposed by Descamps et al: At admission: complete blood count, ALT, AST, total bilirrubin, GGT, alkaline phosphatase, sodium, potassium, creatinine and creatinine clearance, 24h urine protein and urinary eosinophil count, CPK, LDH, ferritin, triglycerides, calcium and PTH, blood glucose, TAP and TTPA, lipase, protein electrophoresis, c-reactive protein, quantitative PCR for HHV-6, 7, EBV and CMV, blood culture, anti-nuclear factor. [68]

Follow up (two times/week): complete blood count, ALT, AST, creatinine, LDH, other laboratory tests according to changes found on admission tests. Evolutive follow up: quantitative PCR for HHV-6, 7, EBV and CMV, complete blood count, ALT, AST, alkaline phosphatase, creatinine, LDH, ferritin and triglycerides.

TREATMENT

The early recognition of adverse drug reaction and withdrawal of the offending drug are the most important and essential steps toward the clinical improvement. Empirical treatment with antibiotics or anti-inflammatory drugs should not be administered during the acute disease, since they may confuse or worsen the clinical picture of patients due to an unexplained cross-reactivity between drugs. [17]

The prognosis is generally worse in the elderly while the recovery is usually faster and complete in children.

For many years, the treatment of DRESS has been based on the use of systemic corticosteroids (dose equal to or greater than 1 to 1.5 mg/kg /day of prednisone or equivalent) with marked improvement of symptoms and laboratory parameters, but several days after the start of treatment. [1, 17, 25] Systemic corticosteroids should have their dose reduced, after the clinical and laboratory control of the disease, slowly over 6-8 weeks in order to prevent a recurrence of the symptoms of the disease. Abrupt deterioration of various symptoms is observed when the withdrawal is accidental or by rapid reduction of the doses of corticosteroids. [17,69] Shiohara et al recommend that all patients should be hospitalized even when the initial presentation is mild. [17]

If symptoms get worse despite the use of oral corticosteroids, other options used in case series are the use of pulsed methylprednisolone (30mg/kg intravenously for 3 days), intravenous immunoglobulin

Table 4: RegiSCAR diagnostic criteria for DRESS/DIHS

Score	-1	0	1	2	MAX	MIN
Fever ≥ 38,5°C	No / U	Yes			-1	0
Enlarged lymph nodes		No / U	Yes		0	1
Eosinophilia:	No / U				0	2
Eosinophils			0.7-1.499 x 10^9L^{-1}	≥1.5 x 10^9L^{-1}		
Eosinophils, IF leucocytes < 4.0 x 10^9L^{-1}			10%-19,9%	≥20%		
Atypical lymphocytes		No / U	Yes		0	1
Skin Involvement:					-2	2
Skin rash extent (% body surface area)		No / U	>50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	No / U				
Organ involvement*:					0	2
Liver		No / U	Yes			
Kidney		No / U	Yes			
Muscle / heart		No / U	Yes			
Pancreas		No / U	Yes			
Other organs		No / U	Yes			
Resolution ≥ 15 days	No / U	Yes			-1	0
Evaluation of other potential causes:						
Antinuclear antibody (FAN)						
Blood culture						
Serology HAV / HBV / HCV						
Chlamydia / Mycoplasma						
*If none positive and ≥ 3 of above negative			Yes		0	1
Total score					-4	9

(IVIG), and plasmapheresis, or a combination of these therapies. [17,70] It should be remembered that the immunosuppressive therapies may increase the risk of infectious complications and sepsis. Mild cases can recover just by drug withdrawal and supportive treatment after a few weeks, even without the use of corticosteroids. However, even in mild cases, the monitoring of liver function tests should be performed and appropriate tests ordered to rule out the involvement of other organs like lungs, thyroid and heart. [17]

Special attention should be given to a possible reactivation of CMV, especially in patients with severe DRESS/DIHS. Physicians should also pay attention to a proper balance between the needs of corticosteroids for relief of symptoms and clinical signs and their possible negative interference on viral load.

High doses of IVIG have two immunological effects: (i) compensates for the decrease in concentration of immunoglobulins in the patient's blood and the defects of the immune protection against HHV-6, (ii) high doses of IVIG have an anti-inflammatory effect that can regulate immune responses, as seen in the treatment of autoimmune diseases. [70]

The group of drug reactions of the French Society of Dermatology published the results of a consensus of experts on the therapeutic management of DRESS/DIHS: [68]

• Absence of signs of severity: topical corticosteroids (potent or very potent), emollients, H1-antihistamines;

• Presence of signs of severity (transaminases > 5 times normal, renal involvement, pneumonia, hemophagocytosis, cardiac, etc.): corticosteroids equivalent to 1 mg / kg per day of prednisone, multidisciplinary evaluation;

• Life-threatening signs (hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, and respiratory failure): steroids

generally associated with intravenous immunoglobulin (IVIG) at a dose of 2 g / kg over five days. The IVIG should not be used without associated steroids. These treatments will be conducted through multidisciplinary evaluation;

• Presence of signs of severity with confirmation of a major viral reactivation: Combining steroids and antiviral (Ganciclovir) and/or IVIG.

Take home messages:

• DRESS/DIHS is an adverse drug reaction caused by an apparent group of drugs, and one third of the cases are related to anticonvulsants, in addition to sulfonamides and allopurinol, which can cause 10-20% mortality.

• The syndrome is characterized by a latency period ranging from 3 weeks to 3 months after the introduction of the offending drug, and its course is marked by apparent sequential reactivation of human herpesvirus and subsequent development of autoimmune diseases, providing an opportunity to establish a connection between viral infections and the emergence of autoimmune diseases.

• In the early DRESS/DIHS hypogammaglobulinemia and reduced peripheral B cell are found and CD4 + CD25 + FoxP3 + (regulatory T cells) are elevated at the beginning of the syndrome, regardless of whether or not the patients are treated with corticosteroids. This clonal expansion of regulatory T cells appears to prevent activation of anti-viral T cells in an appropriate manner and several sequential reactivation of virus is presented in the syndrome. These regulatory T cells have the phenotype $CCR4^+$ and CLA^+, which addresses the skin. In the last stage of the syndrome's activity, phenotype of cytotoxic T cells become prominent and $CD4^+$ lymphocytes become intensely diminished. These cells are depleted over time, suffering apoptosis and becoming reduced after the resolution of the syndrome, which could be a predisposing factor for the development of autoimmunity. ❑

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MAILING ADDRESS:
João de Magalhães Avancini Ferreira Alves
Av. Dr. Enéas de Carvalho Aguiar, 255, 3º andar
Cerqueira César
05403-900 São Paulo, SP
Tel.: (11) 3088-4894 / 3062-5069
Fax: (11) 3088-9145
E-mail: avancini.joao@gmail.com

How to cite this article: Criado PR, Criado RFJ, Avancini JM, Santi CG. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) / Drug-Induced Hypersensitivity Syndrome (DIHS): a review of current concepts. An Bras Dermatol. 2012;87(3):435-49.