Drug reaction with eosinophilia and systemic symptoms (DRESS) and its relation with autoimmunity in a reference center in Mexico*

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Abstract: Background: Drug reaction with eosinophilia and systemic symptoms is a severe adverse drug reaction, with a reported mortality of 10%. Long-term outcomes involve organic failure and autoimmune diseases in some populations.
Objective: To evaluate the clinical prognosis of patients with drug reaction with eosinophilia and systemic symptoms.
Methods: We conducted a retrospective review at a referral hospital in Mexico City in a period of 22 years (1992-2013), looking up for records with diagnosis of DRESS according to RegiSCAR criteria. Clinical characteristics, organ failures, culprit drugs, treatment, and short and long-term sequelae were analyzed.
Results: We found 11 patients with diagnosis of drug reaction with eosinophilia and systemic symptoms syndrome, 7 female and 4 male, with a median age of 22 years-old; 9 had maculopapular rash and 2 were erythrodermic. Affected organs were liver (8/11), kidney (6/11) and hematologic disorders (8/11). The most common culprit drugs were antiepileptic (63%). Systemic corticosteroids were given to 8 patients, being pyelonephritis (1/8) and pneumonia (2/8) the adverse events of this therapy. Long-term sequelae were 1 patient with renal failure, 1 patient with chronic anemia; and 2 patients developed autoimmune diseases (one autoimmune thyroid disease and another one with autoimmune thyroid disease and autoimmune hemolytic anemia). Study limitations: The retrospective nature of the study and the limited number of patients with drug reaction with eosinophilia and systemic symptoms.
Conclusions: Drug reaction with eosinophilia and systemic symptoms syndrome has been linked to the development of chronic organ failure. We found two young patients who developed autoimmune diseases in the short term. Patients with drug reaction with eosinophilia and systemic symptoms should have a long-term monitoring for signs or symptoms suggestive of an autoimmune disease.
Keywords: Autoimmune diseases; Drug eruptions; Eosinophilia

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an idiosyncratic hypersensibility response, characterized in most of the cases by skin rashes (maculopapular rash), beginning usually 2-6 weeks after taking the culprit drug.[1-6] Clinical findings include the presence of eosinophilia or atypical lymphocytes in peripheral blood, lymphadenopathy, fever, or any organ failure.[1,4,7] According to reported series, the most affected organs in order of frequency are skin, liver, kidney, lungs and heart.[1,3,7-9]

The pathogenesis of DRESS syndrome is not fully understood, however the reactivation of human herpes virus 6 (HHV-6), HHV-7, cytomegalovirus, and Epstein-Barr virus has been shown to play a role in the pathogenesis of DRESS.[1,4,10-13] During this viral reactivation, CD8+ T-cells have a significant cell expansion, producing large amounts of IL-2 , TNF-alpha and IFN-gamma, causing the characteristic signs and symptoms of DRESS.[4,8,10,11] These reactive lymphocytes are found infiltrating skin, liver and lungs. A very important fact is the ability of HHV-6 to infect T lymphocytes and produce an immune deregulation altering its function during DRESS, moreover, there is a possibility that this effect is maintained thereafter in all populations of affected lymphocytes, including CD4+ T-cells, CD8+ T-cells and regulatory T-cells.[3,8,10] Regulatory T-cells play a known role in antigens induction and in the suppression of immune response to self antigens. In DRESS, during the early phase, these cells modulate the acute inflammatory response, while in late stages it is hypothesized that the decrease in the number and function of these cells favors the development of autoimmune diseases.[3,14,15]

DRESS mortality rate is of 10%, and in most of the series, this mortality is conditioned by the degree of systemic involvement (hepatitis, nephritis, myocarditis, and pneumonitis) and complications secondary to glucocorticoid treatment.[16,17] Furthermore, as previously mentioned, long term development of autoimmune diseases have been reported, mainly autoimmune thyroid disease and autoantibody production. There are two reports where Ushigome *et al.*[6] and Chen *et al.*[18] found 9% and 5% of patients respectively that

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developed autoimmune diseases, and 44.4% produced autoantibodies even without clinical significance, especially patients who did not received systemic glucocorticoids. [18]

In this report, we evaluate the clinical features and prognosis of patients who developed DRESS syndrome.

METHODS

We conducted a retrospective chart review, looking for expedients with diagnostic report of "DRESS syndrome (drug reaction with eosinophilia and systemic symptoms)", "skin drug reaction", and "systemic allergic drug reaction", from January 1992 to December 2013, at a referral hospital. The diagnostic criteria proposed by International Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score [7] were used to identify cases with a diagnosis of DRESS syndrome. We reviewed the data from those that met the DRESS criteria, also analyzing demographics, clinical characteristics, organ failures, culprit drugs, treatment, and short and long-term sequelae.

RESULTS

We found 251 medical records of patients that had been admitted into our hospital with a diagnosis of adverse drug reaction from January 1992 to December 2013. Using the RegiSCAR score, 11 cases were classified as either definite or probable DRESS syndrome. Of these patients, 4 were men and 7 were women, with a male:female ratio of 1:1.75, and ages ranging from 16 to 49 years, with a median of 22 years **(Table 1)**.

The predominant dermatosis was a disseminated erythematous morbilliform rash, which was present in 9 of 11 patients. The remaining two patients presented erythroderma. Neither patient had mucosal involvement. The median length of the dermatosis was 37 days with a range between 20 to 75 days. Fever was present in 9 patients, ruling out infectious or other causes in all cases. Lymphadenopathy was clinically found in 5 of 11 patients. Organ involvement was hepatic and renal; 8 cases had liver failure, and 6 cases presented renal failure.

In relation to alterations in blood count, 8 had eosinophilia (>0.7 x 10^9 L^{-1} total eosinophils), and 2 patients had lymphocytic morphological changes in addition to peripheral blood eosinophilia.

Anticonvulsant drugs were associated with more frequency, predominantly carbamazepine (5 patients), followed by phenytoin, valproate magnesium, vancomycin, penicillin and allopurinol. The latency period since the start of drug and the beginning of dermatosis was a mean of 37 days (range 7-239 days).

In our series, 8 patients were treated with systemic steroids at a dose of 0.5 to 1 mg/kg. With regard to complications, 3 patients had infections in the short term (2 had pneumonias and 1 had pyelonephritis), all of them in the group of patients who received systemic steroids; one of these patients had complications with severe sepsis and subsequent death.

As for complications following resolution of DRESS, 2 patients developed autoimmune diseases; 1 patient developed autoimmune hemolytic anemia and autoimmune hypothyroidism, and another developed autoimmune hypothyroidism, both belonging to the group of patients not receiving steroid treatment (Table 2).

One was a 29 years-old man who was taking allopurinol during 45 days for hyperuricemia, presented with erythrodermia and who fulfilled the criteria for definitive DRESS, because of that he had to be hospitalized and started intravenous chlorpheniramine. During his stay in the hospital he developed autoimmune hemolytic anemia at day 58 (Hb 6 g/dL, Coombs + IgG and C3, HDL 453 U/L, haptoglobin < 5.8 mg/dL, indirect bilirubin 2.6mg/dL), treated with prednisone and azathioprine. Seventy days after the diagnosis of DRESS in a routine laboratory workup he was found to have autoimmune hypothyroidism (high TSH 27.8 mIU/L, normal T4 12.8 µg/dL, low T3 0.51 ng/dL, high anti-TPO 64 IU/mL), treated with levothyroxine with good control.

The second patient was a 16 years-old woman who was taking carbamazepine for 239 days due to generalized tonic-clonic seizures. She presented with a morbiliform rash and definitive diagnosis of DRESS. She received intravenous chlorpheniramine and acetaminophen. Eight months later, during her follow up, she was found to have tremor, tachycardia and menstrual irregularities, with thyroid functions tests showing slightly elevated TSH 8.5 mIU/L, high T4 122 µg/dL, upper limit T3 2.1 ng/dL, thyroglobulin 5 µg/L and high anti-TPO 80 IU/mL.

DISCUSSION

DRESS syndrome is considered a serious skin reaction along with Stevens-Johnson syndrome and toxic epidermal necroly-

Table 1: Patients characteristics

Age (years), median (range)	22 (16-49)
Sex, n	11
Female	7
Male	4
Skin manifestation, n	
Maculopapular	9
Erythroderma	2
Mucosal affected	0
Latency period, days, median (range)	17 (7-239)
Duration of dermatosis, days, median (range)	37 (20-75)
Signs, n	
Fever	9
Lymphadenopathy	5
Laboratory exams	
Lymphocytosis, cells x 109 L-1, median (range)	13 (2.4-22.9)
Eosinophils, cells x 109 L-1, median (range)	2.5 (0-6.3)
Atypical lymphocytes, n	1
Affected organs	
Kidney, n	6
Liver, n	8
Liver and kidney, n	4
Culprit drug, n	11
Carbamazepine	5
Phenytoin	2
Vancomycin	1
Allopurinol	1
Penicillin	1
Valproate	1
Treatment	
Systemic steroids, n	8
Dose, mg/day, median (range)	50 (10-469)
Adverse events, n	3*

* Secondary to immunosuppression treatment, one patient developed pyelonephritis and two patients had pneumonia.

Table 2: Patients' outcomes

Death, n (cause)	1 (sepsis secondary to pneumonia)
Long term sequels	
Organ failure, n (organ involved)	2 (1 renal failure, 1 chronic anemia)
Autoimmune diseases	2 (1 autoimmune thyroid disease, 1 with autoimmune thyroid disease and autoimune hemolytic anemia)

sis with a mortality rate of 10%.[2,8,19] We present a series of 11 patients with DRESS in the course of 22 years. Some of these diagnoses had to be made retrospectively, since DRESS syndrome was coined in 1996 by Bocquet *et al.*, in an attempt to unify multiple reactions to drugs that seemed to have a common pathophysiological mechanism.[20]

The RegiSCAR criteria are a specific diagnostic tool for DRESS syndrome, which is based on seven clinical and laboratory parameters (fever, sudden onset of dermatosis, lymphadenopathy, other organs involvement, and abnormalities in blood-smear).[7,8,10] Among our patients, 6 were probable cases of this syndrome, and 5 of them had definite diagnosis according to this scale.

Drugs most frequently associated with DRESS syndrome are allopurinol, carbamazepine, phenytoin, dapsone, penicillin and nonsteroidal anti-inflammatory drugs.[2-5,7,9,21] In some reports it has been observed that patients who presented DRESS caused by allopurinol and minocycline have a worse prognosis. In our study, there was a case caused by carbamazepine that had severe eosinophilia (42%, 6384 total eosinophils) and significant increase in transaminases (ALT 1021 IU / L, AST 1911 IU / L), and also presented the longest latency period (239 days after starting taking the drug).

The short and long-term outcomes reported in different cases series appear to be age related. Those associated with renal failure requiring hemodialysis often present in older patients.[2,6,7] In fact, in our series, we had a patient who required hemodialysis, which was 49 years at diagnosis and was the oldest patient in this study.

On the contrary, the development of DRESS in younger patients seems to predict the onset of an autoimmune disease. It has been reported the development of autoimmune diseases months to years after DRESS syndrome. Reported autoimmune diseases are autoimmune thyroiditis, sclerodermiform lesions, diabetes mellitus type 1 (DM1), systemic lupus erythematous and autoimmune hemolytic anemia.[5,6,21-25] One of our patients developed autoimmune hypothyroidism and another one was diagnosed with autoimmune hemolytic anemia and autoimmune hypothyroidism at 58 and 70 days after the diagnosis of DRESS, respectively.

In our reported population, a patient already had the diagnosis of Graves' disease; one patient had systemic lupus erythematous and another had positive anti nuclear antibodies before the development of DRESS. Actually, it is known that about half of patients can have autoantibodies before or at the beginning of DRESS.[6] This leads us to believe that patients with this type of drug reaction have an underlying immune dysfunction that makes them prone to the development of autoimmune or allergic diseases. The patients were female, who presented a morbiliform rash 12-21 days after having taken the drug, with no significant similarities in the laboratory studies during the drug reaction (one with hepatic impairment, one with atypical lymphocytes and marked eosinophilia). The culprit drugs among these patients were carbamazepine and vancomycine. During the follow up, none of them was diagnosed with another autoimmune disease, and this could show that predisposition to autoimmunity plays a role among the autoimmune dyscrasias.

There are not recognized factors that predict the evolution of a patient to the diagnosis of autoimmune disease after DRESS syndrome.[6] In a series of 202 patients who developed DRESS because of sulphonamides or anticonvulsants, 5 had hypothyroidism 4-8 weeks after the drug reaction.[26] Also there is a report of a patient whom presented DRESS after the use of minocycline and subsequently developed autoimmune hyperthyroidism and DM1 and even had markedly elevated ANA, anti-Smith and anti-SSA/Ro without developing other autoimmune diseases.[5]

It has been observed that almost any member of the herpes virus family can be drug re-activated and provoke DRESS, including Epstein-Barr virus, cytomegalovirus, Varicella-Zoster virus, HHV-6 and HHV-7.[3,4,8-11] Although none of our patients was tested in search for HHV-6, one of them presented plasmacitoid lymphocytes, which appear during viral infections, and this could be an indirect sign of a viral infection during the presentation of DRESS syndrome. In fact, it is known that the use of systemic steroids during the episode of DRESS favors the reduction of Epstein-Barr virus titers, and the suspension of this treatment is associated with reactivation of DRESS and a new lift in virus titles.[6,19] Moreover, steroid use is associated with an elevation in the titles of HHV-6 and cytomegalovirus, although it is unknown why this virological profile occurs in patients.[6,10,19]

It is known that autoimmune diseases are more prevalent among young people and middle-aged women. It is said that this population could have a stronger response to any antigenic stimulus, but there is no good answer to why they are more susceptible to autoimmune disease.[27,28] We can emphasize that immunologic response in DRESS raises the possibility in susceptible patients of an imbalance in the immunologic tolerance.

The main treatment includes suspending the culprit drug – this fact remains essential to avoid progression of DRESS and prevent complications from severe disease to other organs.[7] Antihistamines and topical steroids may be used as second line, since symptoms such as itching, xerosis and edema are often debilitating for patients. It is postulated that long-term outcome may be influenced by the duration and type of treatment instituted, reactivation of HHV-6, genetic factors and the presence of underlying diseases.[2,6] The ideal patient for the topical steroid therapy is the one with mild symptoms and mild or none organ damage.

The administration of systemic corticosteroids generally results in improvement of symptoms and laboratory abnormalities, and they are useful in cases where the subject has severe organ damage; nevertheless patients need to be evaluated carefully to rule out any infectious diseases, since DRESS can mimic a wide spectrum of infections (fever, lymphadenopathy, leukocytosis, eosinophilia, morbiliform rash).[25] In our report, patients who received steroid therapy had a systematic evaluation, including thorax x-ray, urine analysis, and previous history of chronic viral diseases (HCV, HBV,

HIV). If the culprit drug is an antibiotic, it is important to protect the patient changing the antibiotic to prevent worsening of the sepsis.

According to observations in a series of 34 patients, those who were not treated with steroids developed autoimmune diseases years later, such as systemic lupus erythematous, autoimmune thyroiditis and new drug reactions, and those who received steroids as therapy did not developed autoimmune disease in the long-term.[6] In this study, we found 2 patients who developed autoimmunity subsequent to DRESS, as none of them had immunosuppressive therapy with glucocorticoids.

The limitations of the study include the retrospective nature of the revision and the few patients with the diagnosis of DRESS.

CONCLUSIONS

In conclusion, DRESS syndrome is a severe drug reaction that has been involved in the development of autoimmune diseases. In some studies, including ours, young patients could have these complications and the pathophysiology of DRESS could explain in part how immune dysfunction produced during DRESS predisposes to autoimmunity. It seems that the development of DRESS is just an epiphenomenon of the predisposition of patients to autoimmune diseases. Evidence suggests that patients with DRESS should have a long-term monitoring for signs or symptoms suggestive of an autoimmune disease.❑

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