Losartan-induced DRESS syndrome

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Abstract

Introduction: drug reactions with eosinophilia and systemic symptoms, known as DRESS syndrome, are a hypersensitivity reaction to medications which can lead to skin lesions and internal organ involvement. This syndrome has typically been associated with a wide variety of medications, including aromatic anticonvulsants, allopurinol and antibiotics as the main culprits.

Objective: we present the case of a patient with DRESS syndrome secondary to losartan, manifesting skin symptoms and mild hepatic involvement. Up until now, there have been no reports of losartan as the cause of this condition. Prompt treatment was instated including the withdrawal of the offending medication and initiation of oral systemic steroids, with a satisfactory response.

Conclusion: caregivers should be alert to the appearance of skin lesions with the use of different groups of medications, not just those typically reported, since any medication could potentially cause a hypersensitivity reaction. **(Acta Med Colomb 2021; 46. DOI: https://doi.org/10.36104/amc.2021.2081).**

Keywords: *DRESS syndrome, losartan, drug hypersensitivity.*

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a drug-induced hypersensitivity reaction which may range from mild illness to potentially fatal cases, and includes skin abnormalities, hematological abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy and internal organ (such as kidney, liver and lung) involvement (1). The current recommendation is to refer to this entity as "drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms" (DiHS/DRESS) (2).

The incidence of this disease has been reported to be 0.9-1 per 1,000-10,000 drug exposures (3, 4). A review of the literature which included 131 articles and 172 patients found that the drugs most frequently associated with this disease were carbamazepine (27%), allopurinol (11%), lamotrigine (6%), phenobarbital (6%), sulfasalazine (6%), phenytoin (4%), and abacavir (3%), among others, with a mean onset after initiating the drug of 3.6 weeks and a range of 0.5 to 8 weeks (5).

Pathophysiology

Several characteristics have been found to indicate that this is a hypersensitivity reaction, such as its reproducibility with skin tests, recurrence of the disease with re-exposure to the triggering drug, and the need for prior sensitization (6).

The proposed diagnostic criteria for this entity are those recommended by RegiSCAR: 1) Acute rash, 2) Drug-related reaction, 3) Hospitalization, 4) Fever >38°, 5) Laboratory abnormalities (at least one): lymphocytosis (>4,000) or lymphopenia (<1,500), thrombocytopenia (< 100,000), eosinophilia (>700), 6) Involvement of >1 internal organ, and 7) Enlarged lymph nodes at >2 sites; with the first three being required for diagnosis, along with three of the following four.

We believe this case report is important, as it deals with a rare disease which generally presents after administering anticonvulsants, but for which, in Colombia, there are no data regarding its association with losartan. Its relevance lies in the fact that losartan is a medication prescribed on a daily basis for treating high blood pressure.

Case presentation

A 62-year-old male patient was admitted to the emergency room due to a 10-day history of widespread erythematous, scaly, itchy lesions over the face, chest, abdomen and extremities (Figure 1). In the review of systems, he reported no cold symptoms, no fever, no joint pain, and a history of high blood pressure being treated for the past month with losartan 50 mg/po every 12 hours. He had taken enalapril previously but was switched because of isolated coughing episodes. He had no other significant medical history. On admission he had the following vital signs: blood pressure: 130/80, heart rate: 80 beats per minute, respiratory rate: 16 breaths per minute, saturation: 99%. A positive finding was morbilliform erythema on his lower extremities

and trunk along with scabbed, erythematous lesions on his jaw, ears, back and the back of his legs. Labs were drawn (Table 1) showing eosinophilia, along with elevated liver function tests and LDH. He was admitted for suspected DRESS syndrome. Since these lesions appeared after the change in medication, losartan was discontinued, and steroid treatment was begun, with subsequent improvement in the lesions. Follow up paraclinical tests were drawn which showed decreased eosinophils and transaminases. A skin biopsy was performed (Figure 2), which confirmed the diagnosis of losartan-induced DRESS syndrome.

Discussion

When DiHS/DRESS syndrome is discussed, we think of a drug-related hypersensitivity reaction, mainly to anticonvulsants since, historically, these have most commonly been reported to cause this condition. It should be noted that various groups of drugs have been reported in different cohorts and case reports as new etiological agents. Thus, in 2011, a review of the literature reported 44 responsible drugs, of which only one, captopril, was an antihypertensive (5). In the RegiSCAR registry, 19 etiological agents were found, none of which was an antihypertensive (7). Other than anticonvulsants, allopurinol, antibiotics, antitubercular medications and NSAIDs stand out (7, 8).

Table 1. *Laboratory results.*

	Day 1	Day 6 (follow up)
Leukocytes	9,550/ul	6,050/ul
Neutrophils	5,190/ul	4,310/ul
Lymphocytes	1,120/ul	850/ul
Eosinophils	2,640/ul	370/ul
Basophils	10/ul	10/ul
Hemoglobin	13.6 g/dl	12.9 g/dl
Platelets	240,000/ul	182,000/ul
Aspartate aminotransferase	116 U/l	45/ul
Alanine aminotransferase	198 U/l	127/ul
Lactate dehydrogenase	507 u/l	269/ul
ESR	8 mm/hour	
CRP	3.81 mg/dl	
Urea nitrogen	8.2 mg/dl	
Creatinine	0.8 mg/dl	
HIV	Negative	
VDRL	Nonreactive	

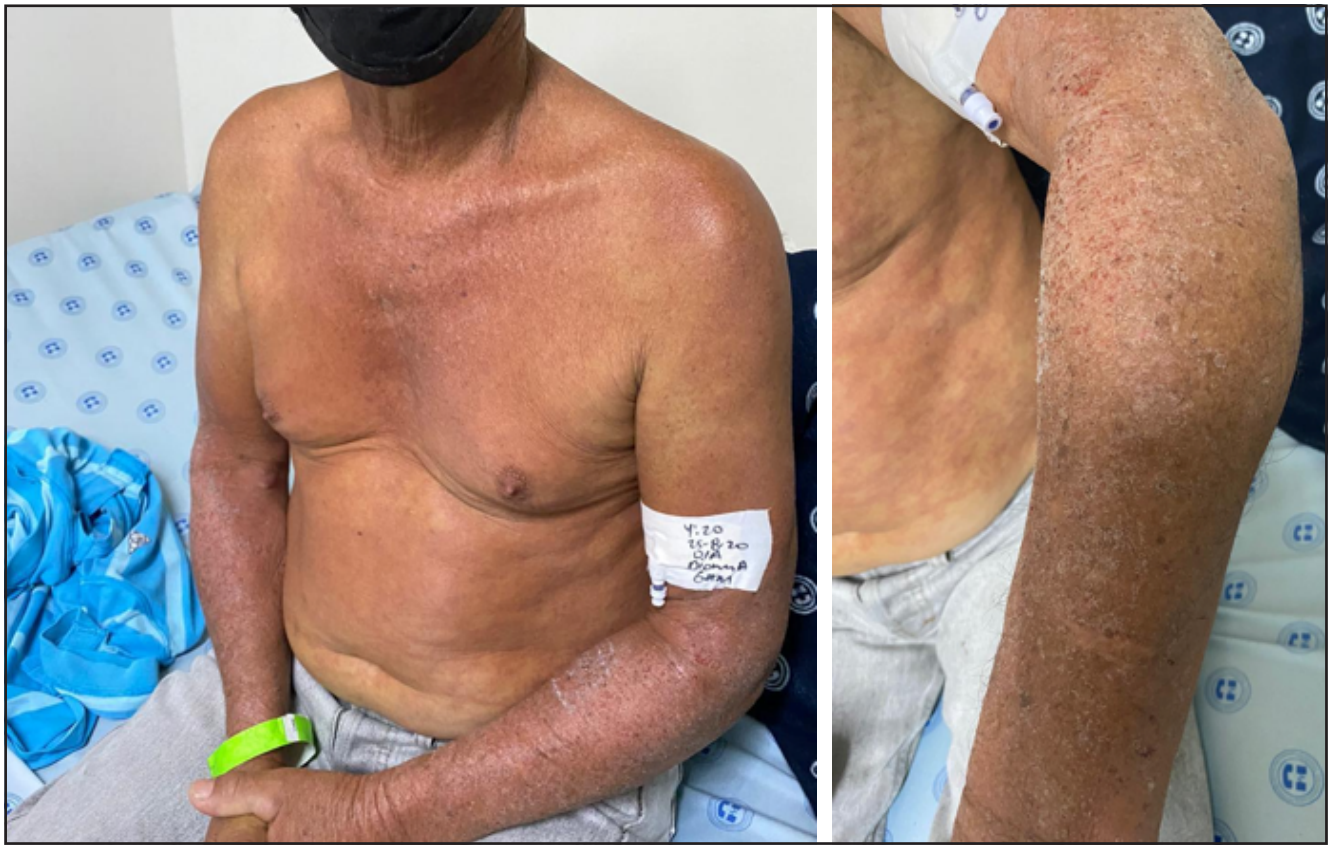


Figure 1. *Widespread erythematous, scaly, itchy lesions involving the face, chest, abdomen and extremities.*

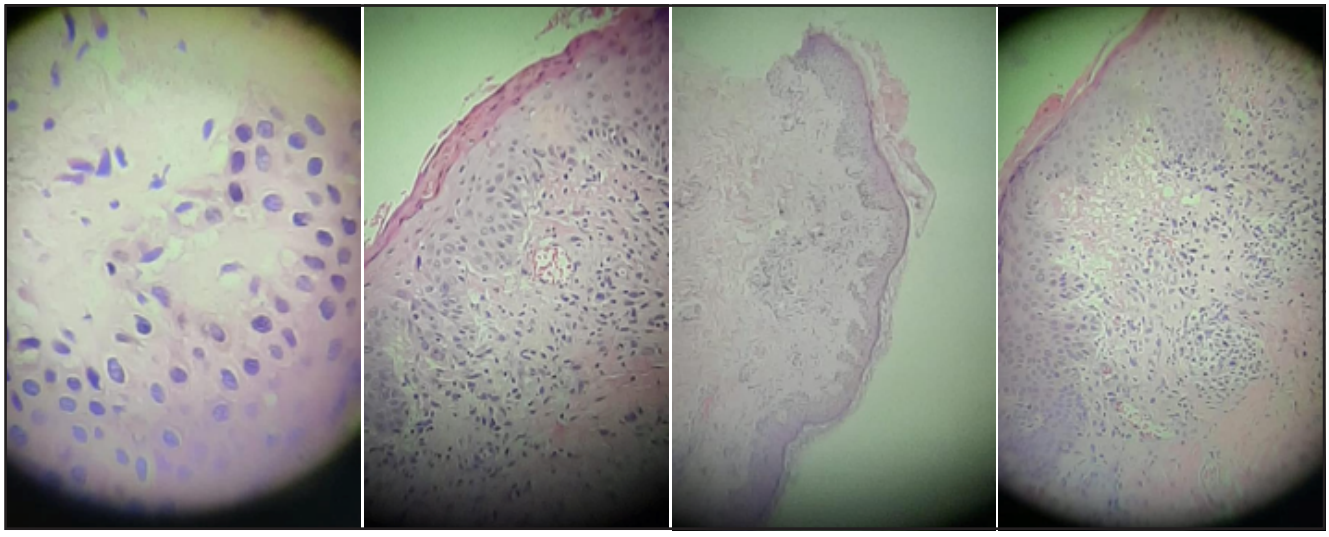


Figure 2. *Skin biopsy of the chest and forearm. Superficial lymphocytic perivascular infiltrate associated with vascular changes in the basal layer associated with the presence of scattered perivascular and interstitial histiocytes, plasma cells and eosinophils, with papillary dermal edema, spongiosis, mild acanthosis with basket-weave orthokeratosis, and parakaratotic foci. Findings compatible with a drug-induced morbilliform rash.*

An important point regarding this condition is the time frame; in our patient, the lesions began 20 days after changing his medication. It has been noted that latency (the time elapsed from the start of the drug to the onset of symptoms) may vary according to the drug group, with 33 days for carbamazepine, 30 days for allopurinol, 27 days for antitubercular agents, 20 days for vancomycin, 18 days for NSAIDs, and 15 days for cephalosporins (8). The time frame has also been used to determine that a DRESS syndrome is unlikely if the medication was started more than three months ago, it has been discontinued for more than 14 days, or it was started less than three days ago (7).

The clinical presentation varies, sometimes beginning with a febrile syndrome, which may present in 50-100% of patients. It may also be accompanied by a pharyngitis-like prodrome which progresses to a widespread macular, morbilliform or target skin rash which then coalesces and becomes itchy. Among the skin lesions, maculopapular rashes occur in 91-100% of cases, while vesicles, mucosal involvement or flaking occur in less than 30%. Enlarged lymph nodes may be present in 4-60% (8). Occasionally, a relapse may occur three to four days after discontinuing the drug responsible, which leads the clinician to think it is an infectious event and begin unnecessary antibiotic treatment which may even cause cross reactions and worsening of the condition. Therefore, acute phase reactants like procalcitonin and C-reactive protein (CRP) have been used to differentiate between bacterial infection and DRESS syndrome, finding that patients with concomitant infectious processes have elevated levels of reactants, using a cut-off for procalcitonin of 1.33 ng/ml and for CRP of 10.83 ng/ml (9). This is important in the clinician's decision-making process, especially in reference to antimicrobial treatment.

When faced with a patient with possible DiHS/DRESS syndrome, the first step is to determine the probable drug responsible. In our case, we were faced with a patient who had been taking enalapril for seven months and had been switched to losartan due to poor tolerance of the first drug. It should be noted that the responsible drug is identified in up to 80%, but in the remaining 20% there is no clear drug, especially when the patient is taking several medications at the same time. Various methods have been proposed for determining the diagnostic probability, and therefore diagnostic criteria have been proposed for both DiHS and DRESS (previously mentioned), although RegiSCAR has its own scoring system to separate the cases into: definite, probable, possible and excluded (7). Paraclinical findings are important, especially eosinophilia (95% of cases), leukocytosis (95%), atypical lymphocytes (35%) (5, 7) and, in some cases, elevated transaminases (10). As previously mentioned, a relationship has been found between the condition and reactivation of viral diseases, such as human herpes virus (HHV)-6, HHV-7, Epstein-Barr virus (EBV) and cytomegalovirus. It is thought that viral reactivation may be related to more severe disease, organ involvement and a prolonged disease course (11). Although a strong association has been found with HHV-6, its presence is not needed to diagnose the disease. Internal organ lesions include liver involvement with elevated liver function tests and hyperbilirubinemia; kidney involvement with elevated serum creatinine, decreased glomerular filtration rate, hematuria, urinary sediment changes and even the need for renal replacement therapy; and pulmonary, gastrointestinal and cardiac involvement (7).

There are no available clinical trials to show which evidence is best for treating the disease. The first step is to discontinue the drug responsible for the disease. Then

a topical steroid may be chosen in mild cases, or where no internal organ involvement is found. This could include betamethasone propionate or clobetasol propionate, applied once or twice a day (12). In 2019, Mizukawa et al. (13) proposed a scale to determine the severity of the disease and predict cytomegalovirus infection reactivation (Table 2, Figure 3); points are added up and the disease is mild if the score is ≤0, moderate if it is 1-3 points, and severe if it is ≥4 points. Applying this scale to our patient, he meets the condition of erosive lesions involving 10-29% of the total body surface area, which gives a score of 1 and classifies it as a moderate disease. Therefore, oral systemic steroid treatment was begun, with resolution of his symptoms as well as improved paraclinical exams (Table 1). Other treatments using immunoglobulin have been tried, although it seems a relationship has been found between the use of immunoglobulin and the appearance of polyglandular syndrome type III in pediatric patients (14),

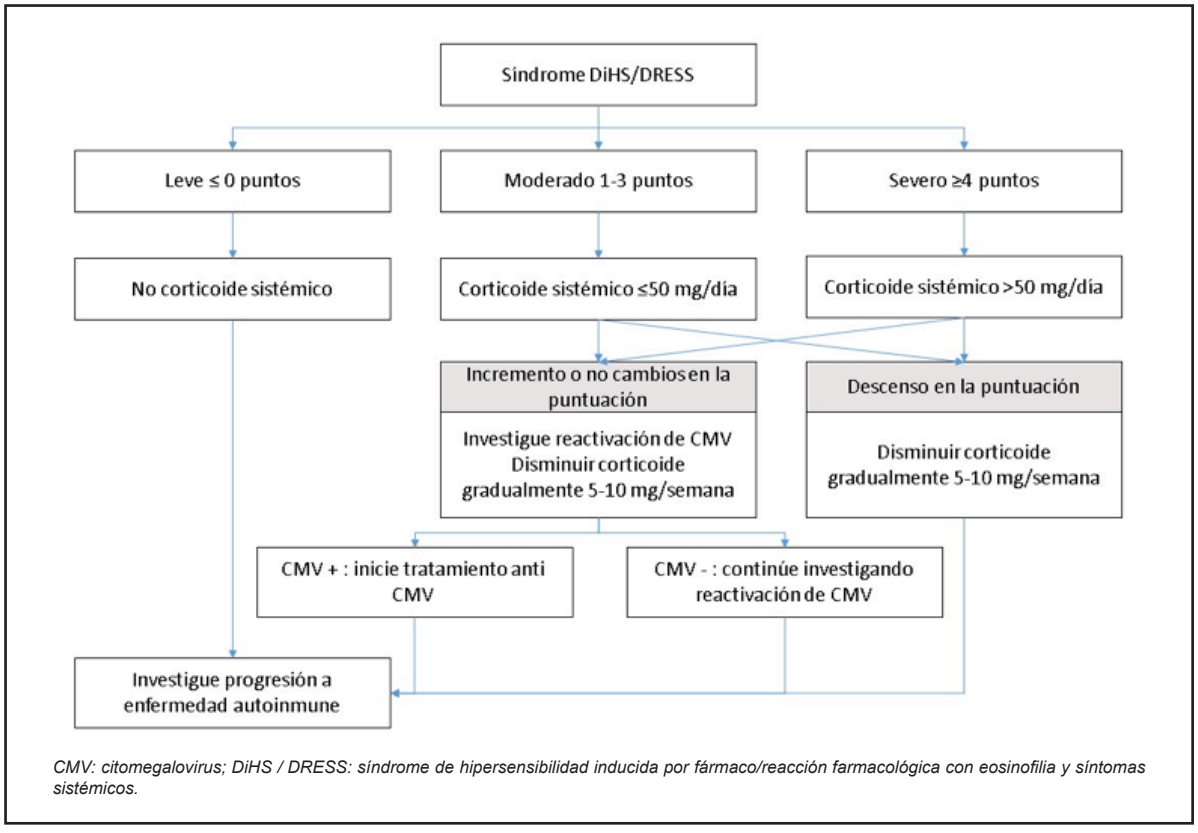
Conclusion

Drug-induced hypersensitivity syndrome/DRESS is a disease which has been associated with many drugs, some of which are more closely related to the occurrence of the disease. In this case, we report this condition associated with a drug which to date we have not known to be causally related, and therefore we emphasize the need to be alert to skin lesions and carry out a detailed review of the

Table 2. *Scale for determining the severity of drug-induced hypersensitivity syndrome and predicting disease outcomes.*

Parameters	-1	1	2	3
Fixed parameters				
Age (years)	≤ 40		≥ 75	
Length of exposure to the drug after initiation (days)		≥ 7		
Exposure to allopurinol		yes		
Variable parameters				
Use of prednisolone			Pulse	
Skin involvement				
Erythematous rash (% of total body surface area)		≥ 70%	Red man syndrome	
Erosive lesions (% of total body surface area)		10-29%		≥30%
Fever > 38.5° (days)		2-6	≥7	
Loss of appetite in days (consuming ≤70% of the normal amount)		≥ 5		
Kidney dysfunction (creatinine, mg/dl)		1-2		>2 or HD
Liver dysfunction (ALT, IU/l)		400-1,000		>1,000
C-reactive protein (mg/dl)	≤ 2	10-15	>15	

ALT: alanine aminotransferase, HD: hemodialysis. The variable parameters may be measured early (0-3 days after onset) and late (2-4 weeks after onset).



CMV: citomegalovirus; DiHS / DRESS: síndrome de hipersensibilidad inducida por fármaco/reacción farmacológica con eosinofilia y síntomas sistémicos.

Figure 3. *Proposed flow chart for diagnosing and predicting outcomes of drug-induced hypersensitivity syndrome.*

patient's medications, as the withdrawal of the associated drug along with prompt treatment may lead to favorable outcomes and a good prognosis.

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