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Ciprofloxacin Ophthalmic DRESS Syndrome: Case Report

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ABSTRACT

Introduction: Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), also known as drug-induced hypersensitivity syndrome, is a rare severe systemic hypersensitivity drug reaction. Diagnosing DRESS syndrome is challenging due to non-specific manifestations that can make it difficult to recognize. Therefore, addressing and discussing this issue is extremely important, considering the potential lethality of a treatable syndrome.

Clinical case: We describe the clinical characteristics of a 39-year-old female who presented with DRESS syndrome associated with the use of ciprofloxacin ophthalmic. The patient manifested a mild maculopapular rash located in the pelvic limbs with subsequent ascending distribution and generalized erythematoviolaceous affecting four extremities, trunk, facial region and scalp, together with fever and lymphadenopathy. Paraclinical tests revealed leukocytosis and eosinophilia. According to RegiScar's ranking, it scored 6 points, classifying it as the definitive case for DRESS. He concluded a schedule with prednisone 1 mg/kg/day with a slow reduction dose, obtaining a good response to treatment.

Conclusions: DRESS syndrome should be suspected in a patient receiving medical treatment who presents with the following signs and symptoms: rash, fever (38°C), facial edema, and lymphadenopathy. Fortunately, this reaction is usually reversible, with a low incidence of residual damage or mortality, in the case of timely discontinuation of antibiotics and use of topical or systemic corticosteroids.

KEYWORDS: DRESS syndrome, eosinophilia, lymphadenopathies, ophthalmic ciprofloxacin

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INTRODUCTION

We present the case of a 39-year-old female patient diagnosed with DRESS syndrome associated with ciprofloxacin ophthalmicus. The aim of this clinical case is to establish some points of reference in the clinic and dermatological characteristics that help in diagnostic guidance and therapeutic decision-making.

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), also known as drug-induced hypersensitivity syndrome, is a rare severe systemic hypersensitivity drug reaction.[1] Uncommon but not rare, the syndrome is not universally known or easy to recognize and is therefore prone to misdiagnosis. Sometimes called drug-induced hypersensitivity syndrome; It was first described in the 1930s in association with phenytoin and, for many years, was considered related to that drug. In 1996, Bocquet and colleagues introduced the term DRESS to distinguish it from drug-induced pseudolymphoma and other drug reactions that are not associated with eosinophilia. The "R" was originally defined as "Rash", however it was changed to "Reaction", as the extent of the dermatosis is variable.[2,3] DRESS syndrome belongs to type IV hypersensitivity, which typically involves skin with features not seen in urticaria or vasulitis reactions.[4] It is estimated to occur in 1 in 1,000 to 10,000 drug exposures. It affects patients of all ages and usually occurs 2 to 6 weeks after exposure to the offending drug. DRESS syndrome has a mortality rate of approximately 10%. It has a cosmopolitan distribution, affecting any age group, with a predominance in the adult population and a greater inclination towards the female gene.[5]

Medications associated with DRESS syndrome include: phenytoin, carbamazepine, phenobarbital, valproic acid, amitriptyline, fluoxetine, piroxicam, diclofenac, naproxen, ibuprofen, captopril, atenolol, propiuthiouracil, sulfonamides, allopurinol, and some antiviral/antibiotic agents, such as amoxicillin alone or in combination with clavulanate and azithromycin.[6]

Beyond the acute manifestations of DRESS syndrome, this condition is unique because some patients develop late sequelae, such as myocarditis or autoimmune conditions, even years after the initial rash.[7] Patients with DRESS are at risk of long-term sequelae, and long-term longitudinal monitoring for autoimmune sequelae is recommended for these patients. It is classified as a serious skin adverse reaction along with Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis.[8]

Diagnosing DRESS syndrome is challenging due to non-specific manifestations that can make it difficult to recognize. Therefore, addressing and discussing this issue is extremely important, considering the potential lethality of a treatable syndrome. Recognizing the onset of DRESS syndrome and initiating treatment as early as possible is crucial to reducing the risk of mortality and improving prognosis.[9]

CASE REPORT

A 39-year-old female patient from Mexicali, Baja California and resident of Caborca, Sonora. Patient with type 1 diabetes mellitus, systemic arterial hypertension and G3b chronic kidney disease. Current condition begins after surgery for vitrectomy associated with diabetic retinopathy, under management with ciprofloxacin/ophthalmic dexamethasone for 3 days. Subsequently, after four days, the patient presented symptoms associated with upper respiratory tract infection such as odynophagia, pharyngitis, epiphora, and conjunctival erythema. Five days later, the patient presented with dermatosis characterized by the presence of a mild maculopapular rash located in the pelvic limbs with subsequent ascending distribution and generalized erythematoviolaceous affecting four extremities, trunk, facial region and scalp (Figure I, II III), which subsequently intensified together with fever of 38°C and bilateral cervical adenomegaly of 1 cm, painful on palpation. mobile, not attached to blueprints.

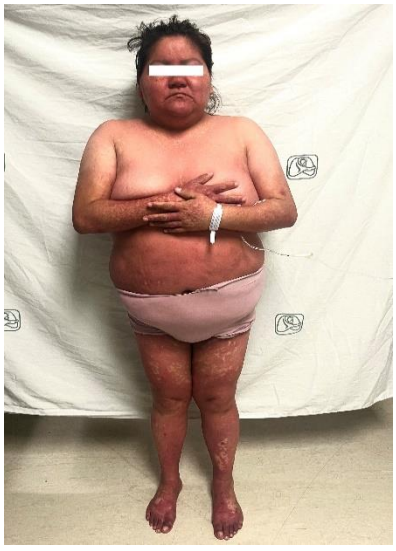

Figure I. Generalized erythematoviolaceous maculopapular rash

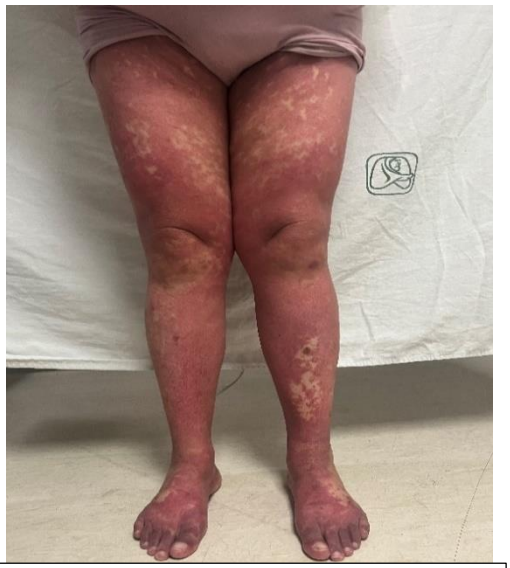

Figure II. Generalized maculopapular rash in both pelvic extremities

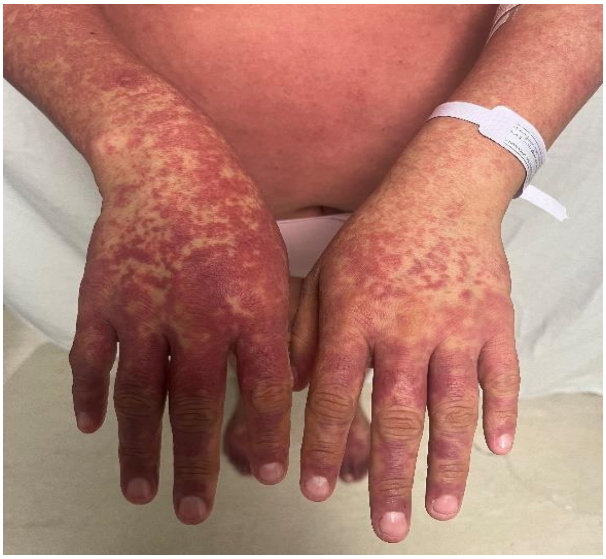

Figure III. Generalized maculopapular rash on both backs of the hands.

She was sent to the General Hospital of Zone No. 5, Nogales, Sonora, where paraclinics were performed who demonstrated leukocytosis 28,600 mm3 at the expense of neutrophilia 21,500 mm3, eosinophilia 1,500 mm3, creatinine 2.4 mg/dL, urea nitrogen 38 mg/dL, urea 81.3 mg/dL, AST 23 IU/L, ALT 46 IU/L, FA 235 IU/L, DHL 472 IU/L, BT 0.2 mg/dL; Chest x-ray with no pathological data. A viral panel was requested, which was non-reactive for HIV, HCV, HBV. Management with systemic corticosteroids was initiated. Evaluation was requested by the Dermatology service, which considered DRESS syndrome associated with ciprofloxacin as a diagnostic possibility, who indicated management with prednisone 1-1.5 mg/kg/day with slow reduction dose.

Report	Age	Sex	Drug	Treatment	Prognosis	Mortality
Descamps et al[2], Laos, 2013	62	Male	Amoxiciline	Corticoesteroids	Good	None
Corneli[4], Brazil, 2017	20	Female	Valproic acid and haloperidol	Prednisone 40 mg/day per 10 days	Good	None
Contreras et al[5], Mérida, 2022	64	Male	Trimetoprim-sulfametoxazol	Prednisone 50 mg/day	Bad	Dead
Sahnoun et al[11], Túnez, 2015	47	Female	Ciprofloxacin	Corticosteroids 60 mg/day	Good	None
Zafar[13], Estados Unidos, 2019	30	Male	Vancomicin	Metilprednisolone	Good	None
Zafar[13], Estados Unidos, 2019	63	Female	Vancomicin	Prednisone	Good	None
Girelli[16], Estados Unidos, 2013	53	Female	Amoxiciline-clavulanic acid	Metilprednisolona 1 mg/kg/day	Good	None
Sharpe[17], Estados Unidos, 2019	52	Male	Oxacilin	Antihistaminics and triamcinolone	Good	None
Hagihara[18], Japón, 2015	76	Female	Anfotericin	Drug suspension	Good	None
Littlehales[19], Reino Unido, 2018	62	Male	Vancomicin	Hidrocortisone	Bad	None
Lee[20], Corea, 2015	71	Male	Isoniacide	Metilprednisolone 2 mg/kg/day	Good	None

DISCUSSION

Drug Reaction Syndrome with Eosinophilia and Systemic Symptoms (DRESS) or Drug-Induced Hypersensitivity Reaction (DIHS) is a severe skin reaction to drugs characterized by the occurrence of fever, rash, lymphadenopathy, involvement of internal organs, and hematologic manifestations, such as eosinophilia and lymphocytosis with or without the appearance of atypical lymphocytes on the peripheral blood smear.[9] This is a rare example of a life-threatening hypersensitivity reaction to type IVb drug involving type 2 (Th2) helper lymphocytes that produce interleukin-4 (IL-4) and IL-5. The latter plays an important role in the differentiation and activation of eosinophils, the hallmark of the disease.[10]

The pathogenesis of DRESS is far from clear, but it occurs with a perfect storm of genetic predisposition (such as HLA-B*13:01 with hypersensitivity to dapsone), drug detoxification enzyme abnormalities (defective enzymes, such as epoxide hydrolase or glutathione transferase, which allow the formation of toxic metabolites), and sequential reactivation of herpesviruses (human herpesvirus 6 or Epstein-Barr virus, followed by human herpesvirus 7 and, finally, cytomegalovirus). Pages 9.10

This interaction is induced by Th2 lymphocytes and CD8+ cells. Th2 cells likely induce type IVb hypersensitivity responses that affect the skin, while CD8+ T cells cause damage to internal organs. In addition, a specific defect in the metabolism and detoxification of a drug may occur in phenotypically susceptible patients. The toxic metabolite then acts as a hapten, initiating an immune response. In other words, genetic polymorphisms of these elimination mechanisms have been implicated in several skin reactions to drugs. [11]

DRESS syndrome is an acute, specific, and severe idiosyncratic drug reaction. Its clinical manifestations are polymorphic. It has an abrupt onset, usually 2 to 6 weeks after the interaction with the offending drug.[12] The disease usually begins abruptly with maculopapular morbilliform rash with fever >38°C, 2 weeks after introduction of the offending drug. Sometimes, there may be an upper respiratory infection similar to a prodrome. Skin lesions usually begin as patchy erythematous macules, pustular target lesions, or eczematous, which may be mildly purpuric and become confluent. The lesions are symmetrically distributed in the trunk and extremities. The most characteristic skin lesions during the early phase are periorbital and facial edema with pinhead-sized pustules, locally simulating generalized acute

exanthematous pustulosis. Lymphadenopathies may be found that favor the cervical, axillary, or inguinal regions. Other symptoms such as bilateral swelling of the salivary glands and severe xerostomia may also occur.[13]

Apart from hematologic abnormalities, liver, renal and pulmonary involvement in descending order are the other most frequently affected organs. Hepatic involvement is the visceral organ most commonly involved in DRESS syndrome and is estimated to occur in approximately 45.0% to 86.1% of cases. The most commonly observed liver abnormality is transaminasemia, but a small subgroup of patients develop fulminant hepatic failure. Renal involvement among patients with DRESS has been reported to range from 11% to 55% of patients, especially with the use of vancomycin. Myocarditis is a rare but fatal complication that can sometimes be under-recognized. Also, encephalitis, aseptic meningitis, myositis, bleeding, thyroiditis, respiratory distress syndrome, pericarditis, pneumonitis, colitis, pancreatitis, hypotension, interstitial nephritis, arthritis, arthralgia, and orchitis as organ compromises that usually occur 1 to 2 weeks after the rash. Pancytopenia is a poor prognostic factor.[14]

The initial criteria for the diagnosis of DRESS syndrome were proposed in 1996, and required the presence of: 1) a drug-induced rash, 2) systemic involvement in the form of lymphadenopathy ≥ 2 cm in diameter or hepatitis (transaminases ≥ 2 times the upper limit of normal) or interstitial nephritis or interstitial pneumonitis or carditis, 3) haematological abnormalities (eosinophilia ≥1.5×109 L − 1 or presence of atypical lymphocytes).[15] The Japan Research Committee on Serious Cutaneous Adverse Reactions (J-SCAR) and the European Registry of Serious Cutaneous Adverse Drug Reactions (RegiSCAR) are the most widely used clinical diagnostic criteria. RegiSCAR appears to be more accurate and comprehensive, but J-SCAR considered viral reactivation as a diagnostic criterion in contrast to RegiSCAR. In addition, there are some other accessories. tools for its confirmation such as the lymphocyte transformation test (LTT), the intradermal test (IDT) and the skin biopsy. The lymphocyte transformation test could not be used for diagnosis, but skin biopsy, in addition to using diagnostic criteria such as RegiSCAR, could be useful. The RegiSCAR was created to rate the severity of adverse skin reactions, and according to the score obtained, it classifies them as "no case", "possible", "probable" or "definitive" definitive case of DRESS syndrome.[16] In the patient, 6 points were found, which correspond to a definitive case. (Table I)

Table 1. RegiScar score for DRESS. Unlikely scenario: 2 points. Probable case: 3-5 points. Final case: 6 points.

RegiScar Score	-1	0	1	2	Case report
Fever >38.5°C	No	Yes			0
Lymphadenopathy		No	Yes		1
Eosinophilia		0.7-1.499x109	>15x109		1
Eosinophilia with leukocytosis >4000		10%, 19.9%	>20%		1
Atypical lymphocytes	No	Yes			0
%SC skin rash	No	>50%			1
Suggestive biopsy DRESS	No	Yes			0
Involved liver	No	Yes			0
Involved kidney	No	Yes			0
Involved pancreas	No	Yes			0
Involved other organs (heart and lung)	No	Yes			0
Resolution >15 days	No	Yes			1
Evaluation of other potential causes: ANA, blood culture, serology for HAV, HBV, HCV, chlamydia, mycoplasma. Yes none positive and > 3 negatives		Yes			1
Total Clinical Case Points					6

Leukocytosis with atypical lymphocytes and eosinophilia of various grades are unique features of the early phase of DRESS, although leukocytopenia may occasionally precede leukocytosis. A recent study by RegiSCAR has shown that transient eosinophilia was present much more frequently (95%) than is commonly reported. However, because eosinophilia can often be delayed for 1 to 2 weeks and even after liver enzyme elevations return to baseline, frequent eosinophilia monitoring may be needed so as not to miss transient eosinophilia. The histopathology of DRESS is relatively nonspecific and consists of a superficial, perivascular, dense, and diffuse lymphocyte infiltrate. Eosinophils may be present, but they are often absent.[17]

DRESS Syndrome is a diagnosis of exclusion. Steven-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, erythroderma, and adult T-cell leukemia or lymphoma are diagnoses that can

present very similarly to DRESS syndrome, and all should be considered before a confirmatory diagnosis is made.[18]

Systemic corticosteroids have been accepted as the standard of care for improving the clinical symptoms of DRESS in the acute phase. Rapid resolution of rashes and fever occurs within several days after starting systemic corticosteroids. Steroids are typically used in the equivalent of 1 to 2 mg/kg daily (once or divided into 2 doses) of prednisone. For severe and/or recalcitrant DRESS syndrome, 2 mg/kg per day (once or divided into 2 doses) is typically used, and less than 1 mg/kg per day may be used for mini-DRESS syndrome.[19]

The French Society of Dermatology formulated guidelines on the management of DRESS as follows: 1) Absence of signs of severity: topical corticosteroids, emollients, and H1 antihistamines. 2) Presence of signs of severity (transaminases > five times normal, renal failure, pneumonia, hemophagocytosis, and cardiac involvement): prednisone 1 mg/kg daily. 3) Life-threatening signs: (hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, respiratory failure): prednisone and IV Ig 2 g/kg for 5 days. 4) Presence of severe signs with confirmation of major viral reactivation: prednisone and valgangciclovir +/− IV Ig. [20]

After stopping the offending drug, most patients take weeks or months to fully recover. The mortality rate among patients with DRESS is estimated to be between 2-10%. The prevalence of sequelae is unknown. Patients are required to be monitored for manifestations of autoimmune diseases, which could lead to chronic organ failure. Long-term sequelae can lead to kidney failure, chronic anemia, autoimmune diseases (autoimmune thyroid disease and autoimmune hemolytic anemia).

CONCLUSIONS

The presence of DRESS syndrome associated with ciprofloxacin ophthalmic in a woman in the fourth decade of life was demonstrated by clinical and laboratory criteria. DRESS should be suspected in a patient receiving medical treatment who presents with the following signs and symptoms: rash, fever (38°C), facial edema, and lymphadenopathy. Fortunately, this reaction is usually reversible, with a low incidence of residual damage or mortality, in the case of timely discontinuation of antibiotics and use of topical or systemic corticosteroids.

A key initial step in the management of DRESS syndrome is withdrawal of the causative medication; Identifying them can be challenging, especially when multiple drugs have been started in recent months and weeks. Delay in identifying them can be detrimental to the patient.

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