DRESS SYNDROME IN THE AGED: A DIFFERENTIAL DIAGNOSIS TO BE CONSIDERED

Síndrome DRESS em idosos: um diagnóstico diferencial a ser considerado

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ABSTRACT

OBJECTIVES: To describe and discuss a rare adverse reaction to drugs diagnosed in an elderly female patient after using levofloxacin and metronidazole: the DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms). **CASE DESCRIPTION:** A 77-year-old elderly woman was diagnosed with pneumonia. After undergoing treatment with metronidazole and levofloxacin, she developed pruritic skin lesions, eosinophilia, and fever. **INVESTIGATIONS:** We established a suspected diagnosis of levofloxacin-induced DRESS syndrome, and therefore we switched the antibiotics and then administered corticotherapy. The patient exhibited rapid and progressive improvement without damage to other organs. **DIFFERENTIAL DIAGNOSIS:** Conditions involving eosinophilia, drug hypersensitivity, and/or skin rash. **COMMENTS:** This syndrome is characterized by skin eruption, systemic symptoms, and eosinophilia. Although the patient did not meet all clinical criteria in the literature, the lack of consensus among authors means that a DRESS syndrome diagnosis could not be ruled out. The condition is rare, but clinicians should be alert to this diagnosis in aged individuals, given its severity and high risk of mortality.

KEYWORDS: drug hypersensitivity syndrome; aged; levofloxacin.

ABSTRACT

OBJETIVOS: Descrever e discutir um efeito colateral incomum às drogas, diagnosticado em uma paciente idosa em uso de levofloxacino e metronidazol: a síndrome DRESS (*Drug Rash with Eosinophilia and Systemic Symptoms*). **DESCRIÇÃO DO CASO:** Uma idosa de 77 anos, diagnosticada com pneumonia, em tratamento com metronidazol e levofloxacino, desenvolveu lesões pruriginosas em pele, eosinofilia e febre. **INVESTIGAÇÃO:** Foi estabelecida a hipótese diagnóstica de síndrome DRESS induzida por levofloxacino e, portanto, foram trocados os antibióticos e administrada corticoterapia. Houve melhora rápida e progressiva, sem comprometimento de outros órgãos em todo o processo. **DIAGNÓSTICO DIFERENCIAL:** Condições envolvendo eosinofilia, reações adversas a drogas e/ou lesões cutâneas. **COMENTÁRIOS:** Esta síndrome é caracterizada por erupção cutânea, sintomas sistêmicos e eosinofilia. Apesar da paciente não preencher os critérios clínicos existentes na literatura, por não haver consenso entre os autores, não se pode descartar completamente o diagnóstico de síndrome DRESS. Apesar de incomum, é importante estar atento para esse diagnóstico em idosos, dado a gravidade e o alto risco de mortalidade.

PALAVRAS-CHAVE: síndrome de hipersensibilidade a medicamentos; idoso; levofloxacino.

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OBJECTIVES

The objectives of the present report were to discuss and describe a rare adverse reaction to drugs diagnosed in a female aged patient using levofloxacin and metronidazole: the DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms).

CASE DESCRIPTION

A 77-year-old mulatto woman, with past medical history of stroke, blood hypertension, systolic heart failure, poliomyelitis, and dependence in activities of daily living, presented symptoms of mental confusion, excessive sleepiness, fever, cough, and dyspnea. We established a diagnosis of pneumonia and started treatment on levofloxacin 750 mg/day, associated with metronidazole 500 mg every eight hours the following day, due the possibility of bronchoaspiration.

The condition evolved after five days with diffuse erythematous-edematous, pruritic plaques (Figure 1), eosinophilia, and 38^{0}C fever. Prednisone (20 mg/day) treatment was introduced.

Two days later, vesicles appeared on her forearm and we observed ulceration in her cheek mucosa.

INVESTIGATION

The Dermatology team assessed the patient, who suggested a possible levofloxacin-induced DRESS. The corticoid dose was raised to 40 mg/day, the antibiotics levofloxacin and metronidazole were switched to amoxicillin (500 mg) and clavulanate (125 mg every eight hours). Dexchlorpheniramine (6 mg every eight hours) was introduced and topical corticoid with fludrocortisone was applied twice/daily.

This resulted in a rapid and progressive improvement in the lesions, eosinophilia and diffuse scaling (Figure 1). Corticoid was progressively withdrawn over a one-month period.

Laboratory findings did not show involvement of organs functioning (Table 1).

DIFFERENTIAL DIAGNOSES

Differential diagnosis include exfoliative dermatitis, viral eruption, vasculitis, allergic diseases, angiolymphoid hyperplasia with eosinophilia, collagen vascular diseases, atopic dermatitis, eosinophilic toxocariasis, eosinophilic pneumonia, malignancy with secondary eosinophilia (e.g. Hodgkin disease, acute myeloid leukemia M4 with bone marrow eosinophilia), parasitic infections and drug hypersensitivity, especially anticonvulsants, semisynthetic penicillin, and allopurinol.

COMMENTS

Skin eruptions are the most common adverse effects of drugs, which severity can range from a mild clinical to severe or fatal condition. Identifying severity markers can be pivotal to the therapeutic decision.[1-3]

The DRESS syndrome is a rare drug reaction characterized by diffuse, pruritic, morbilliform skin eruption that can evolve

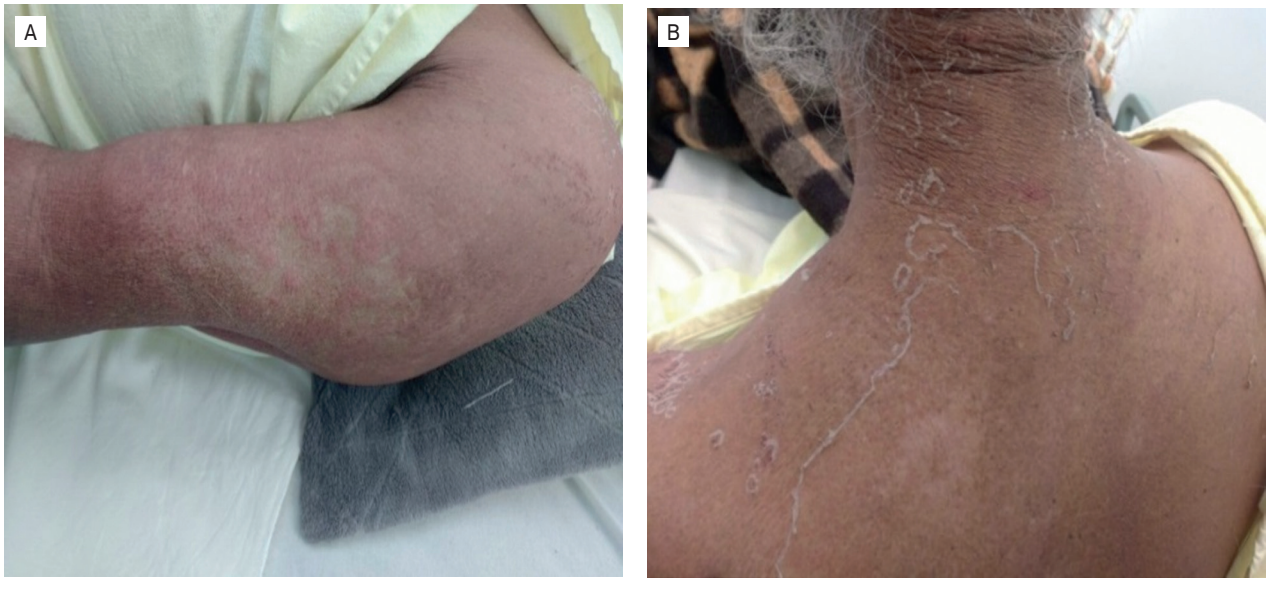

Figure 1. Left image depicts erythematous plaques on forearm. Right image depicts scaling on back after introduction of treatment.

Table 1 Results of laboratory tests during hospitalization.

	Reference values	Day 1	Day 2	Day 3	Day 6	Day 9	Day 11	Day 15
White blood cells	4,000 - 11,000/mm³	12,970	8,800	6,200	12,990	24,100	16,500	7,200
Neutrophils	2,120 - 7,370/mm³	11,198	7,304	4,670	10,166	20,730	14,400	5,913
Eosinophils	80 - 440/mm³	241	238	330	1,494	1,210	460	12
Lymphocytes	920 - 3,630/mm³	1,065	880	998	783	1,210	1,171	907
ALT/TGP*	9-52 U/L	13				27	26	31
AST/TGO#	14-36 U/L	32				22	25	30
Bilirubin	0.2 - 1.3 mg/dL		1.1	0.8		0.9	0.6	0.4
Creatinine	0.7 - 1.2 mg/dL	0.4	0.5	0.5	0.4	0.6	0.5	0.4
Urea	15 - 37 mg/dL	27	45	41	23	43	56	29

*ALT: alanine aminotransferase; #AST: aspartate aminotransferase.

to scaling dermatitis, associated with systemic symptoms – fever, eosinophilia and/or multiple organ damage. The syndrome can also be associated with herpesvirus reactivation.[4-9]

Although eosinophilia can be found in mild skin reactions, some studies have associated it with a more severe form of the disease, exuberant skin reaction, need for systemic therapy, as well as with prolonged hospital stay and recovery.[1-3] Eosinophilia also plays a central role in the DRESS syndrome diagnosis.

The time elapsed between drug exposure and emergence of symptoms typically ranges from two weeks to two months.[4-9] Time to remission tends to be longer compared to more common drug reactions. Although there is no consensus, several authors have devised diagnostic criteria (Tables 2, 3 and 4).[7-9]

Treatment entails immediate withdrawal of the suspected drug and administration of systemic corticotherapy with prednisone at 1 mg/kg/day or equivalent, which should be gradually withdrawn.[5,6,10] Mortality is around 10%, predominantly due to liver necrosis.[5,10] In the long-term, there may be an association with autoimmune events.[4,6]

Anticonvulsants are the most frequently involved drugs[4-6], with few reports of cases induced by fluoroquinolones[11,12]

Table 2 Diagnostic criteria for DRESS syndrome by the J-SCAR group†.

1. Maculopapular rash developing > three weeks after starting therapy with a limited number of drugs
2. Lymphadenopathy
3. Fever (> 38ºC)
4. Leukocytosis (> 10 thousand/mm³)
Atypical lymphocytosis
Eosinophilia
5. Liver abnormalities (ALT > 100 U/L)
6. Human herpesvirus-6 reactivation

†: Five out of six criteria required for diagnosis. Adapted from Shiohara et al.[7].

Table 3 Diagnostic criteria for DRESS syndrome by Bocquet et al.*

1. Skin eruption due to drug
2. Blood abnormality
Eosinophilia ≥ 1,500 mm³
or presence of atypical lymphocytes
3. Systemic involvement
lymphadenopathies ≥ 2 cm in diameter
or hepatitis (transaminase value ≥ 2 N)
or interstitial nephritis
or interstitial pneumonitis
or carditis

*All criteria required for diagnosis. Adapted from Bocquet et al.[8]

Table 4 RegiSCAR-Group Diagnostic Scoring System.

Criteria	No	Yes	Unknown
Fever > 38.5ºC	-1	0	-1
Enlarged lymph nodes (≥ 2 sites, > 1 cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia	0		0
700 – 1,499 or 10 – 19.9%		1	
≥ 1,500 or ≥ 20%		2	
Skin rash	0		0
Extent > 50%	0	1	0
At least two: edema, infiltration, purpura scaling	-1	1	0
Biopsy suggesting DRESS	-1	0	0
Internal organ involved	0		0
One		1	
Two or more		2	
Resolution in > 15 days	-1	0	-1
At least three biological investigations done and negative to exclude alternative diagnoses	0	1	0

Final score: < 2: no case; 2 – 3: possible case; 4 - 5: probable case; > 5: definite case. Adapted from Roujeau et al.[9].

or metronidazole,[5] whose most common adverse reactions include gastrointestinal symptoms and headache.[13,14]

Based on literature, the case reported had characteristics consistent with DRESS syndrome – fever, skin rash and eosinophilia, besides evidence that quinolones can induce the syndrome.

Although the patient did not fully meet the criteria required for the diagnosis according to the J-SCAR[7] group (Table 2), she fulfilled only one (skin rash) of the three essential diagnostic criteria suggested by Bocquet et al.[8] (Table 3). In addition, the patient scored only one point on the RegiSCAR[9] group scoring system (Table 4), which was of undoubting importance to consider DRESS syndrome as a differential diagnosis since the signs and symptoms were related to an aged patient whose organs functions are often impaired or weakened.[15]

Limitations in the present study were the absence of viral serologies and no skin biopsy. In addition, the patient had used ciprofloxacin two months earlier and therefore a delayed reaction to this drug could not be ruled out. This would support the possibility of a DRESS syndrome diagnosis – although studies suggest that quinolones induce symptoms earlier, within 10 days of drug exposure.[11,12] Furthermore, the possibility that the syndrome was induced by metronidazole cannot be ruled out, even though it is unlikely given the scant evidence for this association in the literature.

In the case reported, considering a DRESS diagnosis was prudent in view of the rapid progression of the patient's skin lesions, presence of eosinophilia suggesting severity, and risk of the condition worsening due to an uncertain diagnosis and failure to administer early treatment. Although the clinical criteria in literature were not met, there is no consensus among authors, and therefore the DRESS syndrome could not be ruled out in this clinical case.

The condition is rare, but clinicians should be alert to this diagnosis in the aged, considering its severity and high risk of mortality. In addition, the medical literature on DRESS syndrome in aged individuals is scarce, especially in Brazil.

CONFLICT OF INTERESTS

The authors declare there were no conflict of interests.

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