BAOJ Pediatrics

Noemia Rosado da Silva, et al., BAOJ Pediat 2016, 2: 4
2: 022

Case Report

DRESS Syndrome Secondary to Amoxicillin and Clavulanic Acid - A Pediatric Case Report

Noemia Rosado da Silva[1], Rita Aguiar[2], Laura Azurara[3], Rudi Fernandes[4], Anabela Lopes[2] and Ana Margarida Neves[5]

[1]Departamento de Pediatria Médica do Centro Hospitalar do Algarve EPE – Unidade de Faro, Portugal

[2]Departamento de Imunoalergologia do Centro Hospitalar Lisboa Norte – Hospital de Santa Maria, Lisboa, Portugal

[3]Departamento de Pediatria Médica do Hospital de Sao Francisco Xavier, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal

[4]Faculdade de Medicina da Universidade de Lisboa, Portugal

[5]Departamento de Alergologia Pediatrica do Centro Hospitalar Lisboa Norte – Hospital de Santa Maria, Portugal

Summary

This scientific article aims to describe the case of a 31-month-old child with DRESS syndrome. Given the rarity of this disease in the pediatric population, almost always associated with significant morbidity and mortality, we intend to draw attention to the early recognition and treatment of DRESS, which are crucial for the child's final prognosis.

Abstract

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare syndrome, which involves a severe hypersensitivity drug-induced reaction. It is characterized by the occurrence of an exanthematic polymorphic rash, fever and multiorganic dysfunction. This syndrome is particularly rare in children.

The authors describe the case of a 31-month-old child with sudden onset of a generalized maculopapular erythematous rash, associated with pruritus, fever and angioedema, on the 8th day of amoxicillin-clavulanate oral treatment. Laboratory tests presented atypical lymphocytosis, elevated liver enzymes and increased urine protein/creatinine ratio. Serological tests were positive for Epstein-Barr virus infection.

The diagnosis was based on the clinical history and skin biopsy (which was suggestive of an adverse drug reaction) and was confirmed by skin tests for suspected drugs. The early recognition of DRESS syndrome, the immediate suspension of the suspected drug and the implementation of support measures improved the patient's prognosis, with no associated morbidity or mortality.

Keywords: Adverse drug reactions; Children; DRESS syndrome

Introduction

Adverse drug reactions (ADRs) are an important health problem in pediatrics. In a review of 17 prospective studies, ADRs were the main cause of admission in 2.1% of hospitalized children, 39.3% being life-threatening. The overall incidence of this entity was 9.5% in hospitalized children and 1.5% in the outpatient group [1].

DRESS syndrome is a rare and potentially fatal ADR, with a 10% estimated mortality rate [2]. Patients often present with morbiliform rash, fever, hematological abnormalities and signs of multiorganic dysfunction [2].

Its pathophysiological mechanism is not yet clear, but it is generally regarded as a type IV b hypersensitivity reaction to drugs and their reactive metabolites. However, a number of genetic polymorphisms and the reactivation of *Herpesviridae* family members have also been implicated [3,4].

Case Report

A 31-month-old male caucasian child presented to the emergency department with a sudden onset of rash and fever, following the 8th day of treatment with oral amoxicillin-clavulanate, for a traumatic facial lesion.

The patient had normal developmental milestones and fulfilled the national immunization program. His past medical history highlighted: a *Kingella spp* septic arthritis of the tibiotarsal joint at the age of 24 months, and allergic rhinitis. He had no previous history of allergic drug reactions.

The patient presented a maculopapular, pruritic and erythematous rash, which was initially limited to the face and trunk, but suffered further generalization with palmoplantaris involvement. He also presented centrofacial edema and tongue angioedema. Ocular membranes were not involved, and no lymphadenopaties or organomegalies were described. He presented low grade fever (38ºC) which was responsive to antipyretics.

The initial complementary evaluation revealed lymphocytosis with 6% reactive lymphocytes, elevated liver enzymes (alanine

***Corresponding author:** Noemia Rosado da Silva, Centro Hospitalar do Algarve EPE - Unidade de Faro, Servico de Pediatria, Rua Leao Penedo, 8000-386 Faro, Portugal, Tel: +351 910 170 591; Email: noemialexandra@sapo.pt

Rec Date: September 27, 2016, **Acc Date:** October 5, 2016, **Pub Date**: October 6, 2016.

Citation: Noemia Rosado da Silva, Rita Aguiar, Laura Azurara, Rudi Fernandes, Anabela Lopes and Ana Margarida Neves (2016) DRESS Syndrome Secondary to Amoxicillin and Clavulanic Acid - A Pediatric Case Report. BAOJ Pediat 2: 022.

aminotransferase (ALT) 440 U/L; aspartate aminotransferase (AST) 139 U/L), lactic dehydrogenase (LDH) 976 U/L and total IgE 208 U/mL (Normal <87 U/mL). Specific IgEs were negative for β-lactam antibiotics. The urinalysis showed increased protein/creatinine ratio (>500 mg/g). Serological tests for *Epstein-Barr virus* (EBV) were positive for Anti-VCA-IgG, Anti-VCA-IgM and Anti-EBNA-IgG. Serological tests for *Cytomegalovirus*, *Parvovirus, Herpesvirus* type 1, 2, 6 and 7, and *Mycoplasma pneumoniae* were negative.

The diagnosis of ADR secondary to antibiotic therapy was established and the patient was admitted to the hospital. Amoxicillin-clavulanate was immediately suspended and treatment with prednisolone and hydroxyzine was started.

The histopathological exam of the skin biopsy revealed necrosis of an isolated keratinocyte in the epidermis, spongiosis of the superficial dermis and perivascular lymphocytic infiltrate with eosinophils (Figure 1), suggestive of an ADR.

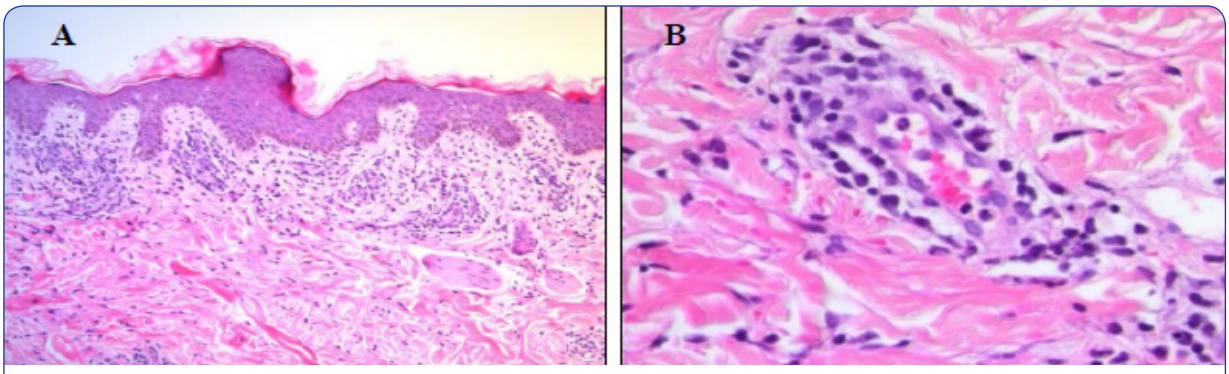

Figure 1: Skin lesions biopsy: skin unchanged only with isolated necrosis of one keratinocyte (Fig.1A); edema of the superficial dermis with perivascular lymphocytic infiltrate with some eosinophils (Fig.1B). (Images courtesy by Prof. Soares de Almeida and Dr. Maria Sanches).

On the fifth day of hospitalization, the patient showed significant clinical improvement and was discharged home. At two weeks follow up, the laboratory results were back to normal. Atopy patch tests (APTs) to β-lactam antibiotics showed a positive reaction to amoxicillin at 48 hours. At six months follow up, the patient maintains β-lactam antibiotics eviction, without clinical or laboratorial alterations.

Discussion

Recent studies attribute great importance to Herpes virus reactivation in DRESS pathogenesis [4]. The *Danger model* proposes that, in the presence of viral replication, the co-stimulatory and pro-inflammatory molecules are up regulated, and this "alert" state causes an activation threshold decrease, predisposing to a T-cell mediated response against the drug [3]. According to the *heterologous immunity model,* a cross reaction between memory virus-specific T-cells and HLA-drug-hapten complexes triggers viral reactivation [5]. Picard et al showed that populations of CD8+ T-cells recognized EBV epitopes in DRESS patients [4].

Infectious Mononucleosis (IMN), frequently caused by EBV, has often clinical and laboratorial similarities with DRESS. Blood tests show atypical pleomorphic lymphocytes, which correspond to activated T lymphocytes, and elevation of liver enzymes. In children with IMN, amoxicillin can induce a skin *rash* similar to that presented by our patient. These facts support the participation of EBV in DRESS pathogenesis.

Several explanatory models of hypersensitivity reactions mediated by T-cells (*p-i concept*) emphasize the importance of the interaction of certain drugs with the human leukocyte antigen (HLA) and T-cell receptors [3].

In a pediatric population study, an association with antibiotics was found, mainly with trimethoprim–sulfamethoxazole (33%) and amoxicillin (10%) [6].

Maculopapular rash is the most common feature of DRESS, usually preceded by fever and pruritus. It progresses to a generalized and infiltrative form, with facial edema. Mucous membranes are usually only mildly involved, in the form of cheilitis or oral cavity inflammation. After the acute phase, the rash becomes violet, with progressive scaly skin [7]. Multiorganic involvements allow differentiation of DRESS from other ADRs. Liver, kidney and lung are the most frequently affected organs [7].

Atypical lymphocytes are characteristic of this syndrome (63% of cases) although leukocytosis or leukopenia, neutrophilia, monocytosis, eosinophilia and thrombocytopenia were also described [7].

If DRESS is suspected, skin lesions should be promptly biopsied. Spongiosis and keratinocytes necrosis are the most frequent findings in the epidermis. Dermis usually contains a perivascular lymphocytic infiltrate and eosinophils are frequently present [7].

Provocation tests are the gold standard for the confirmation of the culprit drug. A good sensitivity for the diagnosis of non-immediate drug allergy to amoxicillin [7] was demonstrated, but its use is contraindicated in severe cases, like DRESS syndrome.

APT is a great diagnostic procedure in these cases, because it is not associated with severe reactions [8]. Although the diagnostic value of APTs is still under investigation [8], a prospective study of 2014 [9] demonstrated the excellent sensitivity of these tests in the diagnosis of non-immediate allergic reactions to amoxicillin.

Because of its high positive predictive value but low negative predictive value, a positive APT is a good indicator of inflammatory hypersensivity reaction, but a negative result does not exclude it [8].

Lymphocyte transformation test (LTT) is a procedure that quantifies T-cell activation in response to drugs. For non-immediate allergy to β -lactam antibiotics, this test showed approximately 70% sensitivity. LTT is not yet routinely recommended, however it should be considered in cases of severe drug allergy [7].

The only consensus in DRESS treatment is the withdrawal of the suspected drug as early as possible, to limit disease progression. Support measures such as antipyretics and antihistamines are recommended. Systemic steroids are the broadly accepted maintenance therapy [8]. However, this therapy is frequently associated with relapses after tapering. A recent study of 2015 [10] suggests that systemic steroid treatment is not essential for mild hepatitis in DRESS, and also can promote viral reactivation, but more prospective studies are required [10].

In the present report, systemic steroids were used, and no relapses were observed, moreover the child presented an optimal clinical outcome.

DRESS syndrome is very rare in the pediatric population. We emphasize the importance of an early diagnosis, to reduce the associated morbidity and mortality.

References

1. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, et al. (2001) Incidence of adverse drug reactions in paediatric in/out-patients: A systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol 52: 77-83.
2. Husain Z, Reddy BY, Schwartz RA (2013) DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol 68(5): 693.e1-14.
3. Schrijvers R, Gilissen L, Chiriac AM, Demoly P (2015) Pathogenesis and diagnosis of delayed-type drug hypersensitivity reactions, from bedside to bench and back. Allergy And Clin 3(5): 31.
4. Picard D, Janela B, Descamps V, D'Incan M, Courville P, et al. (2010) Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. Sci Transl Med 2: 46-62.
5. Pavlos R, Mallal S, Ostrov D, Buus S, Metushi I, et al. (2015) T cell-mediated hypersensitivity reactions to drugs. Annu Rev Med 66: 439-454.
6. Ahluwalia J, K Abuabara, Perman MJ, Yan BC (2015) Human herpesvirus 6 involvement in paediatric drug hypersensitivity syndrome. Br J Dermatol 172: 1090-1095.
7. Chen Y-C, Cho Y-T, Chang C-Y, Chu C-Y (2013) Drug reaction with eosinophilia and systemic symptoms: A drug-induced hypersensitivity syndrome with variable clinical features. Dermatologica Sin 31: 196-204.
8. Husain Z, Reddy BY, Schwartz RA (2013) DRESS syndrome: Part II. Management and 5 therapeutics. J Am Acad Dermatol 68: 709.e1-9.
9. Ben-Said B, Arnaud-Butel S, Bérarda F, Nicolasa J, Nosbauma A, et al. (2015) Allergic delayed drug hypersensitivity is more frequently diagnosed in drug reaction, eosinophilia and systemic symptoms (DRESS) syndrome than in exanthema induced by beta-lactam antibiotics. J Dermatol Sci 80(1): 71-74.
10. Funck-Brentano E,Duong T, Bouvresse S, Bagot M, Wolkenstein P, et al. (2015) Therapeutic manegement of DRESS: A retrospective study of 38 cases. J AM Acad Dermatol 72: 246-52.