



Letter

Trimethoprim-sulfamethoxazole–induced DRESS syndrome in a 4-year-old child

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a drug-induced hypersensitivity syndrome initially described in association with anticonvulsants, although induction by other drugs has been reported. The criteria include lymphadenopathy, acute rash, fever ($>38^{\circ}\text{C}$), involvement of at least 1 internal organ, and blood cell count abnormalities. Symptomatology tends to be prolonged after discontinuation of the causative drug.¹ The incidence rate is approximately 1 in 1,000 to 10,000 exposures; mortality rate ranges from 10% to 40%. DRESS syndrome is infrequently reported in children, whose cases comprise approximately 2% to 3% of all cutaneous drug reactions.² These reactions occur in patients younger than 18 years in fewer than 10% of cases and almost 30% in cases involving DRESS syndrome ($<1\%$ in those <10 years old). We report the case of a 4-year-old boy with trimethoprim-sulfamethoxazole (TMP-SMX)–induced DRESS syndrome who responded to intravenous corticosteroids.

A 4-year-old fully immunized boy was admitted to the pediatric ward with fever ($>38^{\circ}\text{C}$), erythema, swelling, and pain to palpation of the indwelling area of a Hickman catheter that had been in place for 7 days. It had been inserted for HLA-identical hematopoietic stem cell transplantation secondary to his sickle cell disease. He had a long-term Port-A-Cath since inclusion in a hypertransfusion program.

Cefotaxime and teicoplanin were started for the central vein catheter infection, and he was taken to the operating room. The catheter was withdrawn and the insertion area was drained and washed, with purulent material obtained and sent for culture.

Twenty-four hours after the procedure, there was a report of growth of several bacteria from the blood culture taken through the catheter on admission: methicillin-resistant *Staphylococcus aureus*, *Stenotrophomonas* species sensitive only to TMP-SMX, and *Acinetobacter* species. After these results, treatment with cefotaxime and teicoplanin was switched to vancomycin, piperacillin-tazobactam, and TMP-SMX. Vancomycin was switched to teicoplanin 4 days after its initiation because of difficulties achieving appropriate trough levels. The inflammatory parameters showed improvement in 3 days. The child remained afebrile for 7 days, but on day 11 his fever started to spike above 40°C several times a day, without clinical deterioration or increase of inflammatory parameters levels. High-grade fever continued for 4 days later although the child's clinical condition was not impaired. Assuming an infectious disease, he was continued on TMP-SMX. The pattern of fever showed a regular spike after each infusion of TMP-SMX. Two days later, he developed a widespread erythematous and papular rash that was more intense in the facial area and arms and involved the

palms and soles. There were 3-mm-diameter lesions that cleared with pressure and were neither coalescent nor desquamate. In addition, he developed palpebral and labial edema, submandibular lymphadenopathies, and splenomegaly.

A hypersensitivity reaction was suspected and piperacillin-tazobactam was stopped, along with the initiation of dexamethasone and methylprednisolone. Antibiotic therapy was continued with teicoplanin, and ciprofloxacin was added for the catheter-associated blood stream infection. Twenty-four hours after the exanthema, laboratory test showed elevated transaminase levels (aspartate aminotransferase 204 U/L, alanine aminotransferase 158 U/L, γ -glutamyl transferase 129 U/L) and eosinophilia ($>1,100$ cells/ mm^3). The fever disappeared 48 hours after discontinuing treatment with the antibiotic classically related to DRESS syndrome (mainly TMP-SMX) and implementation of methylprednisolone and dexamethasone, whereas the rash waned progressively until resolution a few days later. At discharge 1 week later, the patient was asymptomatic and laboratory parameters were in the normal range. Oral prednisone was maintained for 2 weeks with ulterior tapering for 2 weeks without recurrence 6 months after the event.

DRESS syndrome is a potentially life-threatening drug-induced reaction that can be observed after the administration of many drugs, with anticonvulsants being the most common cause, although it can be produced by other medication such as antibiotics.³ It is typically observed in adults.

This diagnosis was based on the association with diagnostic criteria proposed by the European Registry of Severe Cutaneous Adverse Reactions or the Japanese Research Committee on Severe Cutaneous Adverse Reaction: fever, maculopapular rash, and hematologic alternations such as eosinophilia and leucocytosis with liver disorders. The criteria do not include immune testing or rechallenge. Because the diagnosis was complete and probable according to the first and second scales, respectively,⁴ this case can be considered DRESS syndrome.⁵

Individuals with specific HLA haplotypes of complex classes I and II are predisposed to develop DRESS syndrome when exposed to certain medications. In addition, the hypertransfusion treatment received by the patient might have an effect on this predisposition.⁶ A type IVb hypersensitivity reaction also has been proposed.⁷

The median interval described from drug administration to the appearance of the symptomatology is 22 days for drugs with probable causality, with differences according to type of drug.⁸ The suspected causative antibiotic in this case, TMP-SMX, has been described as responsible for fewer than 1% of these cases reported in the literature,^{3,5} with an average time before symptoms of 14 days, although this period is highly variable.

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DRESS syndrome usually starts with a nonspecific prodromal symptomatology. Unexplained fever can precede the cutaneous rash: it appears as a widespread, unspecific maculopapular, morbilliform exanthema, which is presented in 95% of patients. Facial edema can occur in up to 50% of cases. The liver is the most frequently affected organ, as occurred in this case, but other organ involvement can occur, with possible development of severe organ dysfunction.

The mainstay of DRESS syndrome treatment is the immediate withdrawal of the suspected causative drug and corticosteroid administration for several days with slow ulterior dose tapering.⁹ Immunoglobulin also has been given as an adjunctive therapy in a few cases, although the mechanism and effectiveness of this treatment have not been elucidated. Although no controlled trials have assessed the efficacy of corticosteroid treatment in DRESS syndrome, immediate action is necessary, especially when internal organ involvement occurs, because the syndrome has a current mortality rate of 10%.¹⁰

In summary, an illustrative case of DRESS syndrome in a young patient has been presented. Because of its low frequency in children, it is crucial to emphasize the importance of having a high index of suspicion when compatible symptomatology develops in a child who is taking medication, especially that most related to this life-threatening syndrome.

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