JPPT | Case Report

A Rare Pediatric Case of Allopurinol-Induced Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) Successfully Treated With Intravenous Immunoglobulins

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Allopurinol-induced drug reaction syndrome with eosinophilia and systemic symptoms (A-DRESS) is a well-described condition in adults, whereas it is uncommon among children. We describe a case of A-DRESS in a 16-year-old male with steroid-dependent nephrotic syndrome. He presented a life-threatening clinical course with persisting fever, skin rash, eosinophilia, lymphadenopathy, distributive shock, and herpesvirus 6 detection. The withdrawal of allopurinol and a combination of intravenous immunoglobulins (IVIGs) and systemic corticosteroids led to the patient's recovery without sequelae. Drug reaction with eosinophilia and systemic symptoms (DRESS) in pediatrics is rare and can present in a severe form. Early diagnosis and timely treatment are critical for prognostic purposes. This report suggests the potentially crucial role of IVIG in the treatment of patients with A-DRESS.

ABBREVIATIONS ADR, adverse drug reaction; A-DRESS, allopurinol-induced drug reaction with eosinophilia and systemic symptoms; CRP, C-reactive protein; DRESS, drug reaction with eosinophilia and systemic symptoms; HHV6, human herpesvirus 6; IV, intravenous; IVIG, intravenous immunoglobulin; MP, methylprednisolone

KEYWORDS allopurinol; drug reaction; drug reaction with eosinophilia and systemic symptoms; immunoglobulins

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening adverse drug reaction (ADR) characterized by cutaneous manifestations, fever, lymphadenopathy, hematologic abnormalities (eosinophilia and atypical lymphocytes), and multiorgan involvement. First described by Saltzstein and Ackerman[1] in 1959 as a drug-induced pseudolymphoma, this condition was named DRESS by Bocquet et al[2] in 1996. The estimated incidence ranges between 1:1000 and 1:10,000 in the population,[3] but it occurs less frequently in children.[4]

Several drugs, such as antiepileptic agents or allopurinol, are described as being causative of DRESS in adults.[5] However, poor data exist about the causes of DRESS in the pediatric ages, referring to limited case reports reporting anticonvulsants, followed by antibiotics[6] as mainly responsible. To the best of our knowledge, only 2 previous pediatric cases of allopurinol-induced DRESS (A-DRESS) are described.[7,8]

DRESS syndrome is defined as a delayed-type hypersensitivity reaction to drugs combining several factors, both genetic and not, although the exact pathogenesis is not widely understood. The first step in the treatment of DRESS is always the withdrawal of the causative drug, then supportive care and steroid therapy in severe cases. The mortality rate for allopurinol-induced DRESS is 25%; thus, an early diagnosis is mandatory for prompt treatment and a positive prognosis.

Here, we present a case of A-DRESS syndrome in an adolescent male with a recent recurrence of nephrotic syndrome who was receiving chronic immunosuppressive treatment.

Case Report

In July 2020, a 16-year-old white adolescent male was admitted to the emergency department for a 2-day lasting high fever (axillary temperature, 39.5°C) with a diffuse skin erythematous maculopapular rash. The patient's weight was 44 kg.

Clinical history was characterized by the recent recurrence of steroid-dependent nephrotic syndrome with acute kidney injury (unexplained rise in serum creatinine concentrations, 1.45 mg/dL, about 3 weeks previously) and treated monthly with chimeric anti-CD20 antibody rituximab (375 mg/m^2/dose, 11th dose on admission). The calcineurin inhibitor tacrolimus was withdrawn 5 days before the admission for an elevated serum concentration of tacrolimus (22.33 ng/mL). The patient was receiving an angiotensin 2 receptor antagonist (losartan tablets, 12.5 mg/day) and an angiotensin-converting enzyme inhibitor (ramipril tablets, 5 mg/day) for hypertension, and a proton pump inhibitor (omeprazole tablets, 20 mg/day), whereas allopurinol (100 mg/day) was started 4 weeks before for the occurrence of hyperuricemia (11.2 mg/dL).

On physical examination, the diffuse erythematous maculopapular rash was observed on the face, back, and both upper and lower extremities (Image, A and B) involving palms and soles. There was no conjunctival injection, and the pharynx was slightly hyperemic with moderate tonsillar hypertrophy. Cervical lymphadenopathy was observed. Laboratory tests (summarized in Table 1) showed a serum creatinine of 1.37 mg/dL, as well as an estimated glomerular filtration rate of 46.7 mL/min/1.73 m^2 according to the revised Schwartz estimate.[9] On day one, C-reactive protein (CRP) was slightly elevated (2.11 mg/dL) and the Monospot test (heterophile antibody test) was negative. Proteinuria (3.4 g/day) due to the recent recurrence of nephrotic syndrome was also found. Serology and DNA polymerase chain reaction for Epstein-Barr virus, cytomegalovirus, parvovirus, adenovirus, measles, and toxoplasma were all negative, whereas polymerase chain reaction for human herpesvirus 6 (HHV6) revealed 260 copies of HHV6-DNA/mL. Blood cultures were negative and the patient had no significant risk factors for a bacterial infection. No significant pathologic pulmonary signs were detected.

Clinical and laboratory findings were suggestive of viral infection, and therefore supportive therapy with intravenous (IV) fluids and antipyretics (paracetamol 15 mg/kg/dose) was administered. On day 2 the fever worsened with multiple daily spikes (>39°C, axillary temperature), CRP increased to 4.5 mg/dL, and his serum creatinine increased to 1.82 mg/dL. During the following night, the patient presented with persistent hyperpyrexia (38°C–39.5°C, axillary temperature), oliguria, and hypotension (blood pressure 73/43 mm Hg). Suspecting a septic shock, a crystalloid bolus was administered with hypotension resolution, and IV antibiotic therapy with amoxicillin-clavulanic acid (25 mg/kg/dose [amoxicillin component] IV every 8 hours) was started. On day 3, the rash became intensely erythematous, with the initial confluence on the face evolving into facial edema. Cheilitis and confluent purpuric lesions involving the entire body surface appeared (Image, C and D).

Clinical laboratory test results included: serum sodium 127 mEq/L, leukocytosis (white blood cells, 12,440/µL) with neutrophilia (absolute neutrophil count, 9240/µL), eosinophilia (1370/µL), and hemoglobin 12.1 g/dL were found, with serum creatinine and blood urea nitrogen stability. The CRP increased to 5.56 mg/dL; serum albumin concentration was 3.0 g/dL. Ferritin was slightly increased (480 mg/dL). Liver function tests and coagulation tests were within the normal limits.

The diagnostic workup revealed a febrile systemic condition (hypotension and renal failure) with skin rash, lymphadenopathy, eosinophilia, and blood HHV6 detection leading to the diagnosis of DRESS. Thus, we stopped the administration of allopurinol, considering that was the only medication recently started. The reaction to allopurinol was defined as probable in accordance with the Naranjo Adverse Reaction Probability Scale (see Supplementary Table).

On day 5, a combined treatment with IV immunoglobulin (IVIG, 1 g/kg) and IV methylprednisolone (MP; 1.3 mg/kg twice a day) was started. The IVIGs were administered for 2 subsequent doses, whereas MP

Image. Evolution of the skin rash from day 1 (A and B) to day 3, when the lesions became purpuric and confluent, involving the entire body surface (C and D).

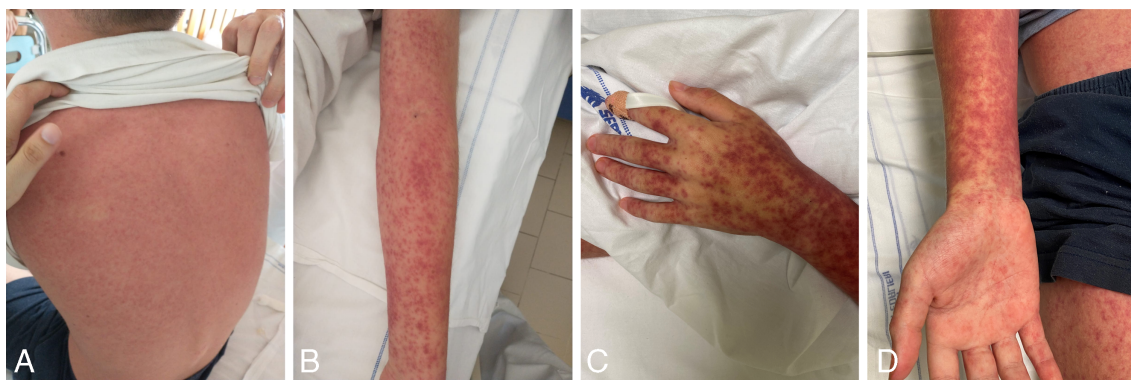

Table. Clinical Signs, Laboratory Values, and Medications During the First 11 Days of Hospitalization

	Days of Hospitalization										
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th
Fever											
Skin rash											
Skin desquamation											
Distributive shock											
Leucocyte count, cells/μL	7730		12,440	11,210	7960	3800	3970	4820	5450	8520	12,420
Eosinophil count, cells/μL	630		1370	1000	340	60	30	20	20	20	50
Creatinine, mg/dL	1.37	1.82	1.51	1.31	1.22	0.84	0.89	0.91	0.79	0.71	0.66
Transaminases, AST/ALT, units/L	16/19		14/15	17/15		43/52	44/60	57/38	32/53	27/51	20/40
C-reactive protein, mg/dL	2.11	4.54	5.56	6.12	6.67	3.52	2.13	1.34	0.87	0.57	<0.46
Procalcitonin, ng/mL			3.53	4.21	100	100	82.56	24.39	6.08	1.99	<0.5
Allopurinol											
Antibiotic											
Intravenous immunoglobulins											
Steroids											

ALT, alanine transaminase; AST, aspartate transaminase

*C-reactive protein and procalcitonin normal values: <0.46 and <0.5, respectively.

was continued for 5 days. Because of the patient's improvement, we converted the MP to oral prednisone (1 mg/kg/dose twice daily). Amoxicillin-clavulanic acid was replaced by a broad-spectrum antibiotic therapy with daptomycin (10 mg/kg/day IV) and meropenem (20 mg/kg/dose IV every 8 hours) because of increased inflammatory markers (procalcitonin >100 ng/mL; CRP, 6.60 mg/dL) and to avoid skin superinfections. On day 6, the fever disappeared, Serum creatinine concentrations normalized (Table), whereas a slight increase in transaminases was observed. According to guidelines for DRESS monitoring in adult patients, echocardiogram, electrocardiogram, and cardiac enzymes were performed and results were normal.

In the following days, the rash gradually improved. First there was desquamation of the face and improvement of lesions of the palms and soles, then there was a resolution of erythrosis and cheilitis. The antibiotics were suspended after 7 days because of the improvement of the inflammatory markers and no growth on blood cultures. The patient was discharged on day 15 with instructions to continue prednisone (1 mg/kg/dose twice daily) for 5 days more, then prednisone was progressively reduced by 5 mg each week. At his primary care follow-up 2 weeks later, the skin lesions appeared completely resolved. No flare-ups occurred during the tapering of steroid therapy.

Discussion

A-DRESS is rare in children, whereas it is more frequently reported in adults,[10] presenting with high severity. Here, we described the first life-threatening case of A-DRESS reported to date in pediatrics. The patient was an adolescent male with a history of steroid-dependent nephrotic syndrome, with a diagnosis given at the age of 18 months, and a recent recurrence of the disease. He presented with fever, skin rash, eosinophilia, lymphadenopathy, and severe systemic involvement up to distributive shock needing crystalloid boluses in urgency. Initial symptoms are fever and rash, which started after 22 days of allopurinol begin. Skin manifestation was characterized by the diffuse morbilliform eruption, associated with facial edema, evocative of DRESS[6] but with an atypical evolution for the presence of purpuric lesions and mucositis (Image). The diagnosis of A-DRESS was made in accordance with the Naranjo

Adverse Reaction Probability Scale, which allowed us to define our case as a "probable ADR" (score 5 of 8; Supplemental Table). The previous reported pediatric A-DRESS cases[7,8] involved a 16-year-old male with a history of arterial hypertension and a 13-year-old female with chronic renal disease. Both showed a prompt clinical response with systemic corticosteroids alone.

The DRESS syndrome is characterized by a type IV hypersensitivity reaction,[11] but its complete pathogenesis is still unclear. It seems to be a result of a complex interweaving of genetic and nongenetic factors. Abnormalities of metabolic pathways, including the slow acetylator phenotype for drugs, have been described.[6] The accumulation of oxypurinol, the active metabolite of allopurinol, could be the cause of A-DRESS and seems to be related to doses between 100 and 300 mg/day.[7] Viral infections, mainly HHV6, play a role in the development of DRESS, even if the pathogenetic mechanism remains not well understood.[11] HHV6 reactivation occurs in 80% of adults with DRESS,[12] whereas it is a rare event in children. In a retrospective study, Ahluwalia et al[13] demonstrated HHV6 positivity (lower limit of detection of 134 copies/mL) in only 4 of 29 children with DRESS,[13] who had a worse disease course, than patients who were HHV6 negative, probably because of significant pulmonary involvement. Thus, they proposed HHV6 as a diagnostic marker. In our case, we detected HHV6 (260 DNA copies/mL) without any significant pulmonary sign.

The main and necessary treatment of DRESS is stopping the suspected drug. Supportive and symptomatic treatments are often necessary (systemic fluids, anti-H1 antihistamines, and emollients), whereas for the severe cases with organ involvement (liver, kidney, lungs, or heart) systemic steroids are recommended.[14]

Given the history of steroidal resistance and the severity of the clinical condition, we decided to start a combined therapy with IVIG and IV MP. Despite the severity of the clinical presentation and the preexisting medical condition, our patient's outcome was favorable without sequelae.

The use of IVIG in pediatric patients with DRESS is reported in the literature in a few clinical cases and is only recommended in combination with systemic corticosteroids.[6] The mechanism of action probably lies in the well-known immunomodulatory effect of IVIG preparations.[15,16] These also contain antiviral neutralizing antibodies that may counteract viral reactivation, including HHV-6, which is described as fundamental in the pathophysiology of DRESS.

For pediatric ages, the diagnostic workup of febrile conditions with important skin involvement should mainly rule out viral exanthemas, staphylococcal or streptococcal shock syndrome, Steven Johnson syndrome, Kawasaki disease, multisystem inflammatory syndrome in children associated with COVID-19, and immunologic and rheumatologic diseases and tumors. Nevertheless, our experience suggests that A-DRESS should be considered in cases of fever, skin rash, systemic symptoms, and a history of recent treatment with allopurinol. The prompt withdrawal of the causative drug and the combined use of immunoglobulins and steroids in our case was effective, leading to a progressive resolution of the cutaneous and systemic clinical picture. This report suggests that IVIGs may have a role in the treatment regimens of DRESS, thus limiting the use of large-dose steroids and their possible adverse effects.

Article Information

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