

DRESS induced by piperacillin-tazobactam in a child

Carlos González Díaz, MD, PhD^a,

Andrés González Hermosa, MD^a,

Eduardo García-Lirio, MD^b,

Rubén Martínez-Aranguren, PhD^c, and

Pedro Gamboa Setien, MD, PhD^b

Clinical Implications

- This case report describes a drug reaction with eosinophilia and systemic symptoms induced by piperacillin-tazobactam. This syndrome is a potential life-threatening drug-induced reaction with very low incidence, but whose appearance is possible in childhood.

TO THE EDITOR:

The drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe delayed adverse drug-induced reaction.

The estimated incidence of this syndrome ranges from 1 in 1,000 to 1 in 10,000 drug exposures.^{1,2} The acronym describes a potentially life-threatening syndrome that includes severe skin eruption, fever, hematological abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement. Drugs that frequently induce DRESS include allopurinol, carbamazepine, lamotrigine, phenobarbital, and sulfasalazine.^{1,2} DRESS has rarely been reported in children with most being caused by antibiotics (vancomycin, minocycline, cefixime, cotrimoxazol, cefotaxime, ampicillin), aspirin, sulfasalazine, naproxen, carbamazepine, phenobarbital, phenytoin, and nevirapine. The reactivation of herpesvirus (human herpesvirus 6 and 7 [HHV-6 and -7], cytomegalovirus [CMV], Epstein-Barr virus) has been suggested to play a role in the pathogenesis of DRESS, although it is unclear if the strong immune activation seen in DRESS is the cause or the consequence of viral reactivation.^{2,3}

We present a case of a child with DRESS induced by piperacillin-tazobactam.

A 13-year-old patient with no previous drug intake and no personal or family history of any previous drug reaction or allergic disease underwent surgery for acute necrotizing appendicitis and peritonitis. His clinical course was unfavorable, presenting with fever, abdominal pain, and biliary fluid output through the surgical wound and the peritoneal drainage. A week later he was operated on again, undergoing a right hemicolectomy and ileocolic anastomosis because of multiple intestinal perforations. After surgery, he entered the pediatric ICU and started treatment with piperacillin-tazobactam and linezolid-fluconazole IV following the protocol for tertiary peritonitis in our hospital. After 5 days, surgery was performed again because of abdominal abscess.

He continued antibiotics and antifungal treatments for 2 weeks and was afebrile for several days. Then, he developed fevers up to 39–40°C, which were poorly controlled with antipyretics (paracetamol). Four days after onset of high fever, facial edema and a maculopapular pruritic skin rash that was widespread and



FIGURE 1. Skin rash affecting more than 80% of the body surface.

confluent, affecting over 80% of the body surface, appeared (Figure 1). No mucosal membrane involvement occurred. One day later cervical, axillary, and inguinal lymphadenopathy appeared, coupled with eosinophilia (37%) (7982 eosinophils/mm³) and increased liver enzymes (aspartate aminotransferase 171 U/L, alanine aminotransferase 370 U/L, gamma-glutamyl transpeptidase 1324 U/L, alkaline phosphatase 366 U/L). There were no atypical lymphocytes, and he had lymphocyte levels of 5%-8% with 1100-1300 lymphocytes/mm³. No changes in renal function, pulmonary, or cardiac involvement were recorded. The skin biopsy showed papillary dermis edema and exsorsis with formation of intraepidermal vesicles and a small number of eosinophils in the epidermis. In the superficial and middle dermis, perivascular and interstitial inflammatory infiltrate was seen, with numerous eosinophils and some lymphocytes.

Suspecting DRESS syndrome we proceeded to discontinue drug treatment (paracetamol, piperacillin-tazobactam, linezolid, and fluconazol) replacing it with dexamethasone, gentamicin, and vancomycin, and parenteral antihistamine and corticosteroid (60 mg prednisolone) treatment was begun. After 5 days, the fever noticeably decreased (37.5-37.9°C fever persisted for one more week), the number of eosinophils decreased (1% one week after treatment with corticosteroids was stopped), and transaminases normalized in the fourth week after the onset of the cutaneous symptoms. The cutaneous symptoms disappeared in 15 days, with skin peeling especially in the limbs. The corticosteroids were stopped in 3 weeks.

The following laboratory tests were performed and were negative: serology against *Salmonella*, *Brucella*, *Shigella*, *Mycoplasma* and hepatitis A, B, and C virus and HIV; PCR HHV-6, CMV, and Epstein-Barr Virus taken in the first and third week (viral serology and PCR) after the onset of the rash; antinuclear antibodies, blood and urine culture. Subsequently, paracetamol tolerance was verified through the administration of 500 mg every 8 hours for 7 days. Previously intradermal skin test and patch tests with paracetamol were performed with negative results.

During admission, the lymphoblastic transformation test (LTT) was performed as previously described. Briefly, lymphocytes, 1.5×10^6 cells/mL, were grown in triplicate for 6 days

TABLE I. Diagnostic criteria for the diagnosis of DRESS syndrome (regiSCAR and Japan diagnostic criteria)

Clinical findings	regiSCAR score ⁶				Japan diagnostic criteria ⁵
	-1	0	1	2	
Fever >38.5°	No/U	Yes			Fever >38°C
Adenopathies		No/U	Yes		Lymphadenopathy
Eosinophilia		No/U			At least one leukocyte abnormality
Eosinophils			0.7-1.49 × 10 ⁹ L ⁻¹	≥1.5 × 10 ⁹ L ⁻¹	Leukocytosis (>11 × 10⁹ L⁻¹)
Eosinophils if leukocytes <4 × 10 ⁹ L ⁻¹			10%-19.9%	≥20%	Atypical lymphocytosis (>5%)
Atypical lymphocytes		No/U	Yes		Eosinophilia (>1.5 × 10⁹ L⁻¹)
Skin involvement					Rash >3 wk
Skin rash extent (% body surface area)		No/U	>50%		
Skin rash suggesting DRESS		U	Yes		
Biopsy suggesting DRESS	No	Yes/U			
Organ involvement					Liver abnormalities (ALT > 100 U/L)
Liver		No/U	Yes		
Kidney		No/U	Yes		
Muscle/heart		No/U	Yes		
Pancreas		No/U	Yes		
Other		No/U	Yes		
Resolution >15 d	No/U	Yes			Prolonged symptoms after drug stopped
Other potential causes					HHV-6 reactivation
ANA					
Blood culture					
Serology					
HAV/HBV/HCV Chlamydia/mycoplasma			Yes		
If none positive and ≥3 of above negative					

HAV, Hepatitis A virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; U, unknown; ALT, alanine aminotransferase; ANA, antinuclear antibodies; HHV-6, human herpesvirus 6.

In bold: clinical data presented by the patient.

with piperacillin-tazobactam (45/5.6 and 4.5/0.56 µg/mL), fluconazole (0.2 and 0.02 µg/mL), and linezolid (20 and 2 µg/mL),^{4,5} only with culture medium as negative control and with phytohemagglutinin (5 µg/mL PHA) as positive control. A stimulation index greater than 2 was considered positive,⁴ and was not reached with any of the drugs.

A month after the patient's release we conducted patch tests with amoxicillin (20%), ampicillin (20%), piperacillin-prazobactam (20%), linezolid (2 mg/mL), and fluconazole (2 mg/mL) with negative results. Afterward we conducted intracutaneous tests with PPL (benzylpenicilloyl octa-L-lysine, 0.04 mg/mL) (Diater Laboratory, Madrid, Spain), MDM (bencilpeniciloate sodium, 0.50 mg/mL) (Diater Laboratory, Madrid, Spain), amoxicillin (20 mg/mL), ampicillin (20 mg/mL), piperacillin-tazobactam (2 to 0.25 mg/mL), fluconazole (0.02 and 0.2 mg/mL), and linezolid (0.2 mg/mL), cefuroxime (2 mg/mL) and ceftriaxone (2 mg/mL) with immediate negative reading for all skin tests. The tests were positive at 24 and 48 hours with PPL, amoxicillin, ampicillin, and piperacillin-tazobactam (erythematous papule with vesicles with a diameter >1 cm), and negative for the other drugs. A biopsy was performed of the intracutaneous test with piperacillin-tazobactam with appearance of infiltrate similar to the one described in the cutaneous biopsy of the initial eruption. LTT was repeated 1 month after his release with piperacillin-tazobactam, fluconazole, and linezolid at the mentioned concentrations with positive results exclusively for

piperacillin-tazobactam 45/5.6 µg/mL with a stimulation index of 2.68 (PHA stimulation index 25.6).

There are 2 diagnostic criteria for DRESS. This case would be classified as atypical DRESS based on the Japanese⁶ criteria because the patient did not show reactivation of HHV-6 (Table I). Regarding the criteria of regisCAR,⁷ a diagnostic tool developed to diagnose DRESS, the patient is included within the group of definite since he presents a score of 7 (Table I).

This case shows some of the typical features of this syndrome: typical symptoms and negative LTT in the acute phase that became positive 3-4 weeks after resolution. This has been reported by the Japanese authors⁶ and that differentiates it from other drug-induced cutaneous disorders such as Steven-Johnson.^{4,6}

Regarding the causal agent, both skin tests and LTT show sensitization to piperacillin-tazobactam, and the skin tests to PPL, ampicillin, and amoxicillin were positive. These data indicate a high possibility of cross-reactivity of piperacillin-tazobactam with other penicillins. The patient had negative *in vivo* tests with other beta-lactams such as ceftriaxone and cefuroxime. We would thus consider using cephalosporins if they were the first line treatment based on future clinical indications.

Systemic corticosteroids are the mainstay of treatment, particularly if they are administered in the earlier stages of the disease, facilitating the resolution of the fever and skin rash. It is necessary to reduce the initial high doses slowly (3-6 weeks) to avoid the appearance of severe flare-ups. The use of other

treatments such as intravenous immunoglobulins or the combination of immunoglobulins with corticosteroids has not shown advantages over the corticosteroids alone. Despite this, corticoids do not help improve other aspects of the disease such as mortality and sequelae within a year. However, because steroids are immunosuppressants, there is a risk of increasing the viral load of HHV-6,7 CMV if present. Therefore, it is advisable to monitor viral load (HHV-6 and -7, CMV) in those patients in whom reactivation is found, to introduce possible antiviral treatment.⁷⁻⁹

DRESS is a severe reaction with a mortality around 10% in published cases.² It is therefore important to try to establish the etiology in these syndromes. In this case, both *in vivo* and *in vitro* tests have proven useful. There have been over 40 drugs collected as triggers of this syndrome.² Previously, a few cases caused by piperacillin-tazobactam have been published¹⁰⁻¹² but none in children.

The patient was diagnosed with DRESS syndrome due to piperacillin-tazobactam, and was advised to avoid penicillins. As an extra precaution, he was also advised to avoid linezolid and fluconazole and use equally efficacious alternatives to these drugs if available because he had also received those medications before the reaction, and their causative role could not be excluded with certainty. If there are no equally efficacious alternatives, then a decision to use these drugs can be made based on the clinical presentation after an individualized risk and/or benefit analysis.

^aServicio de Pediatría, Hospital Universitario de Basurto, Bilbao, Spain

^bServicio de Alergología, Hospital Universitario de Basurto, Bilbao, Spain

^cServicio de Alergología, Clínica Universidad de Navarra, Pamplona, Spain
No funding was received for this work.

Conflicts of interest: The authors declare they have no relevant conflicts.

Received for publication August 29, 2014; revised February 28, 2015; accepted for publication March 16, 2015.

Available online April 11, 2015.

Corresponding author: Pedro Gamboa Setien, MD, PhD, Hospital Universitario de Basurto, Avenida Montevideo, 18, Bilbao 48013, Spain. E-mail: pedromanuel.gamboasetien@osakidetza.net.

2213-2198

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2015.03.008>

REFERENCES

1. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. *Am J Med* 2011;124:588-97.
2. Husain Z, Reddy BY, Schwartz A. Dress syndrome: Part I. Clinical perspectives. *J Am Acad Dermatol* 2013;68:693.e1-14.
3. Pavlos R, Mallal S, Ostrov D, Pompeu Y, Phillips E. Fever, rash and systemic symptoms: understanding the role of virus and HLA in severe cutaneous drug allergy. *J Allergy Clin Immunol Pract* 2014;2:21-33.
4. Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. *Allergy* 2007;62:1439-44.
5. Jurado-Palomo I, Cabañas R, Prior N, Bobolea ID, Fiandor-Román AM, Lopez-Serrano MC, et al. Use of lymphocyte transformation test in the diagnosis of DRESS syndrome induced by ceftriaxone and piperacillin-tazobactam: two case reports. *J Invest Allergol Clin Immunol* 2010;20:433-6.
6. Shiohara T, Takahashi R, Kano Y. Drug-induced hypersensitivity syndrome and viral reactivation. In: Pichler WJ, editor. *Drug Hypersensitivity*. Basel: Karger; 2007.
7. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007;156:609-11.
8. Shiohara T, Kano Y, Takahashi R, Ishida T, Mizukawa Y. Drug-induced hypersensitivity syndrome: recent advances in the diagnosis, pathogenesis and management. In: French LE, editor. *Adverse Cutaneous Drug Eruptions*. Basel: Karger; 2012.
9. Husain Z, Reddy BY, Schwartz A. Dress syndrome: Part II. Management and therapeutics. *J Am Acad Dermatol* 2013;68:709.e1-e9.
10. Calderón O, Fiandor A, Caballero T, Bellón T, Prior N, Lopez-Serrano MC, et al. DRESS syndrome induced by piperacillin-tazobactam in eight patients. *J Allergy Clin Immunol* 2013;131(Suppl). AB 172.
11. Cabañas R, Muñoz L, Lopez-Serrano MC, Contreras J, Padial A, Caballero T. Hypersensitivity to piperacillin. *Allergy* 1998;53:819-20.
12. Carabelli A, Dolcher M, Quartieri F. Utility of patch test in DRESS syndrome. *Allergy* 2008;63:377.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.