Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Probably Induced by Cefotaxime: a Report of Two Cases

Karim Aouam, MD; Amel Chaabane, MD; Adnen Toumi, MD; Nadia Ben Fredj, MD; Foued Ben Romdhane, MD; Naceur A. Boughattas, PhD; and Mohamed Chakroun, MD

We report two cases, one of a 52-year-old man and one of a 32-year-old man, who were treated with cefotaxime. On day 23 and day 28 of the treatment, respectively, the patients manifested clinically with fever, pruriginous skin rash, and facial edema. Blood tests showed marked eosinophilia and atypical lymphocytosis for both patients, and hepatic cytolysis only in the second patient. Cefotaxime was discontinued in both patients; the clinico-biological picture improved gradually and completely disappeared approximately 4 weeks later. Six weeks after complete recovery, both patients underwent intradermal testing which was positive to cefotaxime (2 mg/ml) at the 48-hour reading and negative to benzylpenicillin, amoxicillin, and cefazolin at the 20-minute and 48-hour readings. These clinical pictures suggest drug rash with eosinophilia and systemic symptoms (DRESS) induced by cefotaxime. To the best of our knowledge, only one case of cefotaxime-induced DRESS has been reported in the medical literature. Thus, we add two new cases of cefotaxime-induced DRESS and emphasize the usefulness and safety of intradermal testing in establishing the diagnosis.

Keywords: Cefotaxime; Cross reactivity; DRESS; Skin tests

Corresponding Author:

Karim Aouam, MD
Laboratoire de Pharmacologie
Faculté de Médecine de Monastir
Rue Avicenne
5019 Monastir
Tunisia
Tel: 216-98-67.62.24
Fax: 216-73-46.07.37
Email: aouam_k@yahoo.fr

Received: February 2, 2011

Revised: April 7, 2011

Accepted: June 1, 2011

doi:10.3121/cmr.2011.995

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, idiosyncratic cutaneous reaction to drugs leading to long-lasting skin eruptions in combination with visceral involvement. The hallmark features include a diffuse maculopapular rash, exfoliative dermatitis, facial edema, lymphadenopathy, fever, multivisceral involvement, eosinophilia, and lymphocytosis.¹ Its true incidence is unknown, but it has been estimated to occur at a frequency of 1 in 1000 to 1 in 10,000 exposures to high-risk drugs.² Most of the available DRESS-related literature is in the form of case reports and case series which describe its occurrence with numerous drugs (eg, anticonvulsants, allopurinol, and sulphonamides).³ Beta-lactam antibiotics are rarely implicated in eliciting DRESS. There have been studies suggesting that patch and delayed-reading intradermal tests (IDT) can be effective ways of diagnosing nonimmediate allergic reactions to beta-lactam antibiotics, such as DRESS. Cefotaxime is a cephalosporin that has long been used in neonates, infants, and adults to treat a variety of infections. This drug is known to be associated with rare and mild side effects such as urticaria, skin rash, diarrhea, vomiting, and transient neutropenia.⁴ We report herein two clinical observations of cefotaxime-induced DRESS and suggest the usefulness of IDT in diagnosing this drug side effect.

Figure 1. Photograph of a 6 mm diameter blister demonstrating a positive intradermal test to cefotaxime in Case 1.

Case 1

A 52-year-old man with no known drug allergies was admitted to the infectious disease department for left, post-traumatic retro-orbital cellulitis. He was given intravenous cefotaxime 3 g per day, fosfomycin 4 g per day, and oral ciprofloxacin 1500 mg per day. On day 23 of treatment, the patient developed fever followed 2 days later by an extensive cutaneous rash. On physical examination, his temperature was 38.9°C and a generalized, diffuse, maculopapular, erythematous, petechial, pruritic rash was noted over the face, trunk, and extremities with marked facial edema. He had moderately enlarged tonsils and an injected oropharynx with no cervical lymphadenopathy. Blood tests revealed a white blood cell count (WBC) of $13 \times 10^3/\mu\text{L}$ (eosinophils $0.6 \times 10^3/\mu\text{L}$) with atypical lymphocytes. Lactate dehydrogenase (LDH) and the C-reactive protein (CRP) plasmatic levels were 528 IU/L (normal 50 to 100 IU/L) and 52 mg/dL (normal <1 mg/dL), respectively. Plasmatic liver enzymes, creatine, and creatine phosphokinase (CPK) were within normal limits. The rash was thought to be a hypersensitivity reaction. Cefotaxime was discontinued, and cetirizine 10 mg per day was started. Fosfomycin and ciprofloxacin were continued for 16 days. The rash improved gradually. The WBC was $19.9 \times 10^3/\mu\text{L}$ (eosinophils $1.2 \times 10^3/\mu\text{L}$) at day 12 of cefotaxime withdrawal and became normal at day 28.

Approximately 6 weeks after complete recovery, IDT with cefotaxime, benzylpenicillin, amoxicillin, and cefazolin was performed according to the European Network for Drug Allergy (ENDA) recommendations.⁵ Histamine and saline were used as positive and negative controls. Two healthy controls also underwent IDT with cefotaxime. In the patient, only IDT to cefotaxime (2 mg/ml) at the 48-hour reading was

positive (a 6 mm in diameter blister) (figure 1). The patient manifested no systemic reaction after these tests. In the healthy controls, IDT to cefotaxime was negative.

Case 2

A 32-year-old man with no known drug allergies was admitted to the infectious disease department for infectious endocarditis. He was given intravenous cefotaxime 3 g per day, fosfomycin 4 g per day, and gentamicin 160 mg per day. The gentamicin was stopped after 15 days. On day 28 of treatment with cefotaxime and fosfomycin, the patient developed a generalized maculopapular, erythematous, pruritic rash with facial edema and painful conjunctival hyperemia. Physical examination revealed a body temperature of 39°C with cervical and inguinal lymphadenopathy. Blood tests revealed a WBC of $4.8 \times 10^3/\mu\text{L}$ (eosinophils $0.7 \times 10^3/\mu\text{L}$) with atypical lymphocytes. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) plasmatic rates were at 137 IU/L and 96 IU/L (normal <35 for each), respectively. The patient's LDH and CRP plasmatic levels were at 561 IU/L and 43 mg/dL, respectively. Alkaline phosphatase, gamma glutamyl transferase, creatine, and CPK were normal. The rash was thought to be a hypersensitivity reaction. The cefotaxime was stopped, and cetirizine 10 mg per day was started. Fosfomycin was continued for 11 more days. The rash improved gradually. The WBC was $13 \times 10^3/\mu\text{L}$ (eosinophils $1.2 \times 10^3/\mu\text{L}$) at day 8 of cefotaxime withdrawal and became normal at day 24.

Approximately 6 weeks after complete recovery, IDT with cefotaxime, benzylpenicillin, amoxicillin, and cefazolin was performed according to ENDA recommendations.⁵ Histamine and saline were used as positive and negative controls. Three healthy controls also underwent IDT with cefotaxime. In the patient, only IDT to cefotaxime (2 mg/ml) at the 48-hour reading was positive (figure 2). The patient manifested no systemic reaction after these tests. In the healthy controls, IDT to cefotaxime was negative.

Discussion

We describe two clinical observations of patients who developed cefotaxime-induced DRESS. According to the scoring system by Kardaun et al⁶ to validate the diagnosis of DRESS, scores were 3 (possible) and 5 (probable) in case 1 and case 2, respectively. We believe that cefotaxime was the culprit drug in both patients in view of a clear temporal relationship between cefotaxime administration and the onset of symptoms (23 days and 28 days, typically 2 to 6 weeks),⁷ the remission of the symptomatological pattern after cefotaxime withdrawal, and the positive results to cefotaxime skin tests. Based on the Naranjo algorithm, it is probable that the systemic reaction was due to cefotaxime.⁸ DRESS is a nosological entity mainly characterized by a potentially life-threatening drug-induced cutaneous eruption. It was first described with phenytoin in 1950. Fever, rash, lymphadenopathy, and internal organ involvement with marked eosinophilia constitute the main manifestations. The most frequently involved organ is the liver, followed by the

Figure 2. Photograph demonstrating an intradermal test positive to cefotaxime (CTX) and negative to benzylpenicillin (Peni G), amoxicillin (AMX) and cefazolin (CFZ) in Case 2.

kidney and lung.⁶ Our second patient was diagnosed with DRESS as defined by Kardaun et al,⁸ and in fact, the clinical features were typical: fever, lymphadenopathy, rash followed by exfoliative dermatitis, hypereosinophilia $>1000/\mu\text{L}$, and visceral involvement (hepatic cytolysis). However, these criteria were not completely met in our first patient, since there was no visceral involvement; thus, we consider that this patient manifested a DRESS-like syndrome rather than authentic DRESS. Sulfasalazine and anticonvulsant agents, especially aromatic ones, are most implicated in eliciting this side effect. Conversely, beta-lactam antibiotics are rarely responsible. Only isolated case reports of beta-lactam-induced DRESS are available in the medical literature. Beta-lactam antibiotics known to be associated with DRESS are cefadroxil, ceftriaxone, piperacillin-tazobactam, and recently penicillin V.⁹⁻¹² Cefotaxime is a parenterally administered third generation cephalosporin with a broad spectrum of antimicrobial activity. After more than a decade of use, cefotaxime continues to play an important role in treating patients with serious infections, particularly those caused by Gram-negative bacteria. Cefotaxime is relatively safe compared to other beta-lactam antibiotics, as it is known to cause the fewest adverse reactions.¹³ To the best of our knowledge, only one clinical observation of cefotaxime-induced DRESS has been described in the medical literature

so far. Fujiwaki et al¹⁴ reported a case of an 11-year-old girl who developed DRESS on day 20 of a cefotaxime course. As in the case described by Fujiwaki, the only involved organ in our case was the liver. It was a mild hepatic cytolysis (96 IU/L and 80 IU/L, respectively) with neither cholestasis nor liver failure.

Interestingly, in both of our cases the diagnosis of DRESS was made possible by performing IDT to cefotaxime, which was strongly positive in both patients at the 48-hour reading with no systemic reaction related to the test. Patch tests and IDT are known to be classical devices to investigate delayed drug hypersensitivity, and they seem to have good sensitivity in diagnosing beta-lactam-induced DRESS. As IDT appears to be somewhat more sensitive than patch testing, we used IDT to diagnose the hypersensitivity reactions in our patients. Suswardana et al⁹ reported a case of a cefadroxil-induced DRESS confirmed by patch test. In the patient described by Fujiwaki,¹⁴ the patch test to cefotaxime was positive. Drug skin tests are also useful in assessing cross-reactivity between chemically similar drugs such as beta-lactam antibiotics. The IDT to benzylpenicillin, amoxicillin, and cefazolin was negative, suggesting a selective reaction to cefotaxime. This hypothesis needs to be confirmed by a provocation test in view of the lack of data about the predictive value of these skin tests.

Many articles have reported that DRESS might be associated with human herpes virus 6 (HHV6) reactivation.¹⁵ It seems likely that the activation of monocytes and CD4⁺ T lymphocytes induced by drug allergy also induces HHV6 reactivation. Investigations for HHV6 reactivation were not conducted in our patient, but were negative in the Fujiwaki case.

Conclusion

We add to the medical literature two new cases of cefotaxime-induced DRESS and report that IDT appears to be useful and safe in diagnosing this reaction. Only the liver was involved in cefotaxime-induced DRESS with a mild cytolysis. It seems that there is a lack of cross reactivity to other beta-lactam antibiotics. This hypothesis needs to be confirmed by incidental administration of other beta-lactam antibiotics, as drug provocation test should be avoided in DRESS.

Acknowledgements

The authors are greatly indebted to Professor Adel Rdissi for his help with the language used in this article.

References

1. Kano Y, Shiohara T. The variable clinical picture of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms in relation to the eliciting drug. *Immunol Allergy Clin North Am* 2009; 29:481-501.
2. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med Surg* 1996;15:250-257.

3. Begon E, Roujeau JC. [Drug hypersensitivity syndrome: DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)]. [Article in French] *Ann Dermatol Venereol* 2004; 131:293-297.
4. LeFrock JL, Prince RA, Leff RD. Mechanism of action, antimicrobial activity, pharmacology, adverse effects, and clinical efficacy of cefotaxime. *Pharmacotherapy* 1982;2:174-184.
5. Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, Pichler WJ, Demoly P. ENDA; EAACI. Diagnosis of nonimmediate reactions to beta-lactam antibiotics. *Allergy* 2004;59:1153-1160.
6. Kardaun SH, Sidoroff A, Valeyrie-Allanore, Halevy S, Davidovici BB, Mockenhaupt M, Roujeau JC. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007;156:609-611.
7. Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? *Arch Dermatol* 2001;137:357-364.
8. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-245.
9. Suswardana, Hernanto M, Yudani BA, Pudjiati SR, Indrastuti N. DRESS syndrome from cefadroxil confirmed by positive patch test. *Allergy* 2007;62:1216-1217.
10. Akcam FZ, Aygun FO, Akkaya VB. DRESS like severe drug rash with eosinophilia, atypic lymphocytosis and fever secondary to ceftriaxone. *J Infect* 2006;53:e51-e53.
11. Fahim S, Jain V, Victor G, Pierscianowski T. Piperacillin-tazobactam-induced drug hypersensitivity syndrome. *Cutis* 2006;77:353-357.
12. Doña I, Chaves P, Gómez E, Torres MJ, Cantó LG, Blanca M. Drug rash with eosinophilia and systemic symptoms after penicillin V administration in a patient with acquired C1 inhibitor acquired deficiency. *J Investig Allergol Clin Immunol* 2009;19:325-357.
13. Fekety FR. Safety of parenteral third-generation cephalosporins. *Am J Med* 1990;88:38S-44S.
14. Fujiwaki T, Yoshikawa T, Urashima R, Ishioka C. Drug rash with eosinophilia and systemic symptoms induced by cefotaxime and ampicillin. *Pediatr Int* 2008;50:406-408.
15. Hashimoto K, Yasukawa M, Tohyama M. Human herpesvirus 6 and drug allergy. *Curr Opin Allergy Clin Immunol* 2003;3:255-260.

Author Affiliations

*Karim Aouam, MD**; *Amel Chaabane, MD**; *Adnen Toumi, MD†*; *Nadia Ben Fredj, MD**; *Foued Ben Romdhane, MD†*; *Naceur A Boughattas, PhD**; *Mohamed Chakroun, MD†*

**Pharmacology Department, University Hospital, Monastir, Tunisia*

†Infectious Disease Department, University Hospital, Monastir, Tunisia