Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Probably Induced by Cefotaxime: A Report of 2 Cases

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Abstract

We report two cases of a 52 and 32-year-old males treated with cefotaxime. On day 23 and 28 of the treatment, the patients have manifested a clinical picture of fever, pruriginous skin rash and facial edema. Blood tests showed marked eosinophilia and atypical lymphocytosis for both patients and only hepatic cytolysis in the second patient. Cefotaxime was discontinued and the clinico-biological picture improved gradually to completely disappear approximately 4 weeks later. Six weeks after complete recovery, we performed for both patients an intradermal test (IDT) which was positive to cefotaxime (2 mg/ml) at 48 hour-reading and negative to benzylpenicillin, amoxicillin and cefazolin at 20 minute and 48 hour-reading. These clinical pictures suggest a Drug rash with eosinophilia and systemic symptoms (DRESS) induced by cefotaxime. To our best 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 point out the usefulness and safety of IDT in establishing the diagnosis.
**Introduction**

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 has been estimated to occur at a frequency of 1/1000 to 1/10,000 exposures to high-risk drugs (2). Most of the available DRESS-related literature is in the form of case reports and case series which has described its occurrence with numerous drugs (*e.g* anticonvulsants, allopurinol, and sulphonamides) (3). Betalactams are rarely implicated in eliciting DRESS. There have been studies suggesting that patch and delayed-reading intradermal tests can be effective ways of diagnosing nonimmediate allergic reactions to betalactams, such as DRESS. Cefotaxime is a cephalosporin which has long been used in neonates, infants and adults to treat several infections. This drug is known to be associated with rare and mild side effects such as urticaria, skin rash, diarrhoea, vomiting and transient neutropenia (4).

We report herein, two clinical observations of cefotaxime-induced DRESS suggesting the usefulness of skin tests in diagnosing this drug side effect.
Cases report

Case 1

A 52-year old male with no known drug allergies, was admitted to the infectious disease department for a left, post traumatic retro-orbital cellulitis. He was given intravenous cefotaxime and fosfomycin, 3 and 4 g a day, respectively, and oral ciprofloxacin, 1500 mg a day. On day 23 of this 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 and pruritic rash was noted over the face, trunk and extremities with marked facial edema. He had moderately enlarged tonsils, injected oropharynx with no cervical lymphadenopathy. Blood tests revealed white blood cell count (WBC) of $13 \times 10^9/L$ (eosinophils $0.6 \times 10^9/L$) with atypical lymphocytes. Lactate deshydrogenase (LDH) and the C-reactive protein (CRP) plasmatic levels were at 528 IU/l and 52 mg/l, respectively (normal: 50 to 100 IU/l and <1 mg/l respectively). Plasmatic liver enzymes, creatine, creatine phosphokinase (CPK) were at normal rates. The rash was thought to be a hypersensitivity reaction and cefotaxime was withdrawn and cetirizine 10 mg a day was started. Fosfomycin and ciprofloxacin were continued for 16 days. The rash improved gradually, but WBC was $19.9 \times 10^9/L$ (eosinophils $1.2 \times 10^9/L$) at day 12 of cefotaxime withdrawal and became normal at day 28. Approximately six weeks after complete recovery, an IDT to cefotaxime, benzylpenicillin, amoxicillin and cefazolin was performed according to the European network of drug allergy (ENDA) recommendations (5). Histamine and saline were used as positive and negative controls. Two healthy controls underwent IDT with cefotaxime. Only IDT to cefotaxime (2 mg/ml) at 48 hour-reading was positive (a blister with a diameter of 6 mm) (fig 2). The patient has manifested no systemic reaction after these tests. IDT to cefotaxime was negative in healthy controls.
Case 2

A 32-year old male with no known drug allergies, was admitted to the infectious disease department for an infectious endocarditis. He was given intravenous cefotaxime, fosfomycin and gentamicin 3g, 4 g and 160 mg a day respectively. 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 oedema and painful conjunctival hyperhemia. The physical exam revealed a body temperature at 39°C and cervical and inguinal lymphadenopathy. Blood tests revealed a WBC of $4.8 \times 10^9/L$ (eosinophils $0.7 \times 10^9/L$) with atypical lymphocytes. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) plasmatic rates were at 137 and 96 IU/l (normal: < 35 for both). LDH and CRP plasmatic levels were at 561 IU/l and 43 mg/l respectively. Alcaline phophatase, gamma glutamyl transferase, creatine and CPK were normal. The rash was thought to be a hypersensitivity reaction and cefotaxime was stopped and cetirizine 10 mg a day was started. Fosfomycin was continued for 11 days. The rash improved gradually, but WBC was $13 \times 10^9/L$ (eosinophils $1.2 \times 10^9/L$) at day 8 of cefotaxime withdrawal and became normal at day 24. Approximately six weeks after complete recovery, an IDT to cefotaxime, benzylpenicillin, amoxicillin and cefazolin was performed according to the ENDA recommendations (5). Histamine and saline were used as positive and negative controls. Three healthy controls underwent IDT with cefotaxime. Only IDT to cefotaxime (2 mg/ml) at 48 hour-reading was positive (fig 2). The patient has manifested no systemic reaction after these tests. IDT to cefotaxime was negative in healthy controls.
Discussion

We describe two clinical observations of patients who developed cefotaxime-induced DRESS. According to the scoring system of Kardaun et al. (6) to validate the diagnosis of DRESS, scores were 3 (possible) and 5 (probable) in case 1 and 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 symptoms’ onset (23 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 phenytoïn 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 kidney and lung (6). Our second patient was diagnosed with DRESS as defined by Kardaun et al (8). 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 patient 1 since there was no visceral involvement and thus, we can consider that this patient has manifested a DRESS-like syndrome rather than authentic DRESS. Sulfasalazine and anticonvulsant agents especially aromatic ones are the most implicated in eliciting this side effect. Conversely, betalactams are rarely responsible. Only isolated case reports of betalactam-induced DRESS are available in the medical literature. Betalactams known to be associated with DRESS are cefadroxil, ceftriaxone, piperacillin-tazobctam and recently penicillin V (9, 10, 11, 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 the treatment of patients with serious infections, particularly those caused by Gram-negative bacteria. Cefotaxime is a relatively safe drug compared to other betalactams, it is known to cause the fewest adverse reactions (13). To our knowledge only one clinical observation of cefotaxime-induced DRESS has been described in the medical literature so far. Indeed Fujiwaki et al. (14) reported a case of an 11-year-old girl who developed DRESS on day twenty of cefotaxime course. The only involved organ in our second case and that described by Fujiwaki was the liver. It was a mild hepatic cytolysis (96 and 80 IU/I respectively) with neither cholestasis nor liver failure.

Interestingly, in our cases the diagnosis of DRESS has been made possible by performing an IDT to cefotaxime which was strongly positive in both patients at 48-hour reading with no systemic reaction related to these test. Intradermal and patch tests are known to be classical devices to investigate the delayed type of drug hypersensitivity and they seem to have a good sensitivity in diagnosing betalactam-induced DRESS. As IDT appears to be somewhat more sensitive than patch testing, we used former testing to diagnose the hypersensitivity reactions in our patients. Suswardana et al. reported a case of a cefadroxil-induced DRESS confirmed by patch test (9). Moreover, in the patient described by Fujiwaki, the patch test to cefotaxime was positive. Drug skin tests are also useful to assess cross-reactivity between chemically similar drugs such as betalactams. The IDT to benzylpenicillin, amoxicillin and cefazolin was negative suggesting a selective reaction to cefotaxime. This hypothesis has to be confirmed by a provocation test in view of the lack of data about the predictive value of these skin tests.

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

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

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References


Figure legend

Fig 1: positive IDT to cefotaxime in patient 1.

Fig 2: positive IDT to cefotaxime and negative to benzylpenicillin (peni G), amoxicillin (AMX) and cefazolin (CFZ) in patient 2.