

Drug reaction with eosinophilia and systemic symptoms from ceftriaxone confirmed by positive patch test: An immunohistochemical study

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Clinical Implications

- Ceftriaxone has not been previously reported as a causative drug of Drug reaction with eosinophilia and systemic symptoms syndrome. Patch test can help to prove the etiological role of the culprit drug, and immunohistochemical studies should be advisable to explain the complex immunopathogenesis of Drug reaction with eosinophilia and systemic symptoms.

TO THE EDITOR:

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but severe cutaneous adverse reaction (SCAR) that requires early withdrawal of the causative agent and is characterized by skin rash, fever, hematological abnormalities, and lymphadenopathy with involvement of several internal organs.¹ It has been linked to several common drugs, including anticonvulsants, sulfonamides, allopurinol, and antibiotics. Among these, ceftriaxone has not been previously reported as a causative drug. Specific clinical, biological, and histological findings allow the diagnosis of DRESS syndrome, but the etiologic diagnosis is difficult: many drugs may be involved, allergological *in vivo* and *in vitro* test results are not always positive, and a challenge test is not advisable. Pathogenesis is complex: DRESS syndrome is usually classified as type IVb hypersensitivity (T_H2 cells, eosinophils). Nevertheless, a type IVc hypersensitivity ($CD8^+$ T cell) was hypothesized.^{2,3}

A 66-year-old man was prescribed ceftriaxone (2 g/d) for treatment of L1-L2 vertebral bodies osteolysis related to spondylodiscitis. Three weeks later, he presented widespread infiltrated maculopapular lesions, focally purpuric (Figure 1, A and B) with edema of the face. The overall skin rash extent was less than 50% body surface area. Multiple lymphadenopathies were present. Laboratory tests showed absolute eosinophilia ($3.1 \times 10^9/L$), abnormal renal function (blood urea nitrogen, 155 mg/dL; serum creatinine, 2.01 mg/dL). Other investigations done to exclude alternative diagnosis (antinuclear antibodies, serology for hepatitis A virus/hepatitis B virus/hepatitis C virus, antibodies to Chlamydia/Mycoplasma) were negative. PCR for human herpesvirus 6 was positive in blood (371 copies/mL). Skin biopsy revealed spongiosis, koilocytosis, lymphocyte exocytosis, lichenoid dermal infiltrate with lymphocytes, and eosinophils. Withdrawal of ceftriaxone and therapy with oral ebastine (20 mg/d) and betamethasone dipropionate ointment (0.05%) resolved clinical and laboratory abnormalities in 4 weeks. Based on the RegiSCAR scoring system,² “probable” DRESS syndrome (final score 5: no fever [−1], enlarged lymph nodes [1], eosinophilia $\geq 1.5 \times 10^9/L$

[2], skin rash suggesting DRESS [1], biopsy suggesting DRESS [0], 1 organ involved [1], resolution in > 15 days [0], evaluation of other potential causes [1]) was diagnosed.

Four months after complete healing, patch test (PT) with ceftriaxone sodium 5% in petrolatum was performed with positive result (Figure 1, C). PT was biopsied showing spongiosis, koilocytosis, lymphocytic epidermotropism, and widespread dermal inflammation with lymphocytes, neutrophils, and eosinophils. Ceftriaxone PT was negative in 20 control subjects.

Immunohistochemical study both in exanthema and in PT biopsies was performed. We used mAbs to IL-5 as the main mediator of eosinophilic inflammation of IVb type hypersensitivity; perforin, granzyme B (GrB), fatty acid synthase ligand (FASL) as the main cytotoxic factors of IVc type hypersensitivity; INF- γ on the basis of a $CD4^+$ T-cell–deficient mice that presented drug-specific allergic skin reactions mediated only by antigen-specific INF- γ –producing $CD8^+$ T cells.⁴ Moreover, because our patient presented human herpesvirus 6 reactivation, the cytotoxic markers (perforin, GrB, and FASL) were also studied on the basis of the evidence that human herpesvirus reactivation is related to an expansion of an antiviral $CD8^+$ T-cell response.⁵ We used standardized automated procedures on a Bond Max—automated slide stainer (Vision Biosystems, Mount Waverley, Australia) using the avidin-biotin complex method. The stained sections were evaluated and scored in blinded fashion with a light microscope (Nikon Y-THM, Tokyo, Japan) by 2 independent observers. All tested antibodies were positive in both biopsies, stronger in PT biopsy than in exanthema biopsy (Figure 2).

DRESS syndrome is an idiosyncratic SCAR induced by several drugs.⁶ In literature, sporadic cases of DRESS syndrome due to cephalosporins are described.⁷ To our knowledge, this is the first report of DRESS syndrome caused by ceftriaxone. Moreover, the culprit role of this drug was confirmed by positive PT without any clinical recurrence, as recently stated by Barbaud et al.⁸

Immunohistochemical data on DRESS syndrome are lacking. Our study allows us to speculate about immunopathogenesis of DRESS syndrome, usually classified as type IVb hypersensitivity reaction.⁹ Already in 2005 there was “a dilemma” about DRESS syndrome immunopathogenesis because of the possible involvement of $CD8^+$ lymphocytic mediators, usually involved in type IVc hypersensitivity reaction, such as toxic epidermal necrolysis (TEN). It was hypothesized that the immunopathogenetic mechanism of these SCARs differs quantitatively but not qualitatively.³

In our immunohistochemical study, IL-5 positivity confirms type IVb immunopathogenesis of DRESS syndrome; conversely, perforin, GrB, and FASL positivity comes out in favor of type IVc hypersensitivity (Figure 2). Perforin, FASL, and INF- γ positivity was stronger than IL-5 either in exanthema or in PT biopsies. Despite clinical features and laboratory tests of our patient suggesting a typical DRESS syndrome, our immunohistochemical data led us to downsize the role of cutaneous eosinophilic inflammation and to upsize the role of the cytotoxic proteins produced by cytotoxic T lymphocytes. Moreover, the increase in soluble FASL has been recently identified as an early biomarker of DRESS progression to TEN.¹⁰

In this first reported case of DRESS syndrome induced by ceftriaxone, we confirmed the diagnostic role of PT. Moreover,



FIGURE 1. Infiltrated maculopapular lesions, focally purpuric, of anterior (A) and posterior (B) aspect of the trunk; positive patch test result to ceftriaxone sodium (5% in petrolatum) (C).

	IL-5	Perforin	Antibody to: GrB	FASL	INF- γ
Exanthema biopsy					
Visual score	1+	2+	1+	2+	2+
Patch test biopsy					
Visual score	1+	3+	3+	4+	4+

Visual score for immunohistochemical staining: 0 = no staining; 1+ = mild; 2+ = moderate; 3+ = strong; 4+ = very strong

IL-5: sc-7887, Santa Cruz Biotechnol, Santa Cruz, CA, USA
Perforin: 5B10, Novocastra, Leica Biosystems GmbH, Nussloch, Germany
GrB: AP15585PU-N, Acris GmbH, Luzern, Swiss
FASL: ab15285, Abcam, Cambridge, UK
INF- γ : sc-8308, Santa Cruz Biotechnology, Santa Cruz, CA, USA.

FIGURE 2. Results of immunohistochemical study in exanthema and patch test biopsies.

immunohistochemical data showed similar distribution of a panel of cytokines both in skin lesions and in biopsy of patch test and documented the coexistence of type IVb and IVc hypersensitivity. Nevertheless, based on a single case, our data do not support any postulated mechanism of DRESS and need to be confirmed in a larger patient series affected by DRESS syndrome.

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Conflicts of interest: K. Hansel is on the Novartis and Abbvie Psoriasis boards. L. Stingeni is on the Novartis, Lilly, and Abbvie Psoriasis boards. The rest of the authors declare that they have no relevant conflicts of interest.

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