

Letter to the Editor

Amikacin-induced drug reaction with eosinophilia and systemic symptoms syndrome: Delayed skin test and ELISPOT assay results allow the identification of the culprit drug

To the Editor:

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe allergic syndrome characterized by generalized skin rash, blood eosinophilia, and multiple-organ failure.¹ DRESS syndrome is induced by drug-specific T cells and thus corresponds to a type IV delayed allergic hypersensitivity. Allopurinol, anticonvulsants, and antibiotics are the drugs most frequently implicated. Delayed allergy to aminoglycoside antibiotics is rare and can present as severe Lyell syndrome.² However, no aminoglycoside-induced DRESS syndrome has been reported thus far. We report a case of amikacin-induced DRESS syndrome confirmed by skin and immunobiologic tests.

A 42-year-old man received a multidrug therapy that included clindamycin, amikacin, and vancomycin for septic arthritis of the right knee. Eighteen days after starting treatment, he presented with a maculopapular and edematous skin reaction, facial edema, and fever. Blood tests showed hypereosinophilia upper 8000/mm³ (normal value, <500/mm³), atypical lymphocytes, increased liver enzyme levels (alanine transaminase upper 11 N [normal value, <35 UI]), and coagulation disorder (prothrombin time, 30%; n > 70%). Viral serologic and blood PCR results were negative for all viruses tested, including human herpesvirus (HHV) 6, HHV4 (EBV), and HHV5 (cytomegalovirus), and according to the Kardaun et al³ diagnostic score, which we calculated at 6, we confirmed the diagnosis of DRESS syndrome. Drugs were immediately stopped, and intravenous corticosteroid treatment with prednisolone (60 mg/d) was started. Under this treatment, the patient improved slowly to achieve complete remission within 1 month. Allergologic workup, including patch tests and immunobiologic tests (ELISPOT assay), was performed 6 months after resolution of DRESS syndrome. Amikacin (2.5 mg/mL), clindamycin (15 mg/mL), and vancomycin (50 mg/mL) solutions were prepared by the hospital pharmacy from the intravenous drugs and provided as serum saline solution. Patch tests with 8-mm-diameter Finn chambers were applied on the upper back, and readings were performed at 48 and 72 hours. At both times, amikacin patch test results were strongly positive (++ according to International Contact Dermatitis Research Group criteria, corresponding to a strong edematous/vesicular reaction).⁴ Patch test results to clindamycin and vancomycin remained negative. Histologic analysis of the positive amikacin patch test result showed changes typical of a delayed-type hypersensitivity reaction. The diagnosis of amikacin-delayed allergy was made. At day 4, after installation of the patch test on the skin (24 hours after the 72-hour reading), the patient experienced a generalized skin flare-up without any other organ involvement (normality of renal, hepatic, and blood assay results). Topical steroids, moisturizers, and antihistamines led to complete remission in 7 days. A second series of patch tests to gentamicin, netilmicin, tobramycin, neomycin, mupirocin, and spectinomycin was realized 3 months later to evaluate cross-reactivity with other aminoglycosides and showed positive results

for amikacin only. Thus gentamicin was given to the patient without any adverse reaction.

An IFN- γ ELISPOT was performed to confirm the presence of circulating amikacin-specific T cells. PBMCs were prepared from the patient's blood immediately before patch testing, as previously described.⁵ Briefly, PBMCs were washed in PBS and resuspended at a final concentration of 5×10^6 cells/mL in complete culture medium. ELISPOT assay plates (Human IFN- γ ELISPOT PVDF-Enzymatic; Diaclone, Besançon, France) were coated overnight at 4°C with anti-IFN- γ antibody provided in the kit, blocked with dry skimmed milk for 2 hours at 37°C, and washed 3 times with PBS before use. PBMCs (5×10^5 in 100 μ L) were added on the plates and incubated overnight at 37°C/5% CO₂ in the presence of amikacin (and amoxicillin as a negative control). Plates were then washed 3 times with PBS/Tween 0.1%, incubated for 2 hours at 37°C with a biotinylated anti-IFN- γ antibody, and then extensively washed. IFN- γ spot-forming cells (SFCs) were developed by using streptavidin-alkaline phosphatase, incubated for 2 hours at 37°C, and extensively washed before adding the substrate (5-bromo-4-chloro-3-indolyl-phosphate). The number of IFN- γ SFCs present in each well was counted with a Carl Zeiss vision ELISPOT (Zeiss SAS, Le Pecq, France). Results of the IFN- γ ELISPOT assay were expressed as the numbers of IFN- γ SFCs/10⁶ PBMCs. ELISPOT revealed the presence of circulating amikacin-specific T cells (negative control, 12 SFCs/10⁶ PBMCs; positive control, 213 SFCs/10⁶ PBMCs; amikacin [1 mg/mL], 78 SFCs/10⁶ PBMCs). No T cells specific for clindamycin and vancomycin were detected in the patient's blood.

Skin tests are useful in the management of drug-induced DRESS syndrome diagnosis, as shown here for aminoglycosides and as previously reported for other drug classes, such as anticonvulsants and fluidione.^{6,7} However, patch tests might also be potentially dangerous during DRESS syndrome allergologic assessment, even if disease flare-up was limited to the skin in our case. Thus we suggest that in patients with DRESS syndrome, patch tests must be performed under close follow-up to optimize the management of disease relapse. The usefulness of immunobiologic tests, especially the ELISPOT assay, has been previously reported in nonsevere (maculopapular exanthema) β -lactam-delayed allergies.⁵ Our case suggests that the ELISPOT assay could be helpful to detect circulating drug-specific T cells, to identify the culprit drug, and to select a non-cross-reactive aminoglycoside antibiotic that could be administered safely to patients with DRESS syndrome. Nevertheless, more studies are needed to confirm the value of immunobiologic tests and ELISPOT assays in the management of patients with DRESS syndrome.

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