Overlap Between DRESS Syndrome and Exanthema Induced by Sulfadiazine in a Patient Treated With Sulfamethoxazole: Utility of the Lymphocyte Transformation Test for Identification of the Culprit Drug

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J Investig Allergol Clin Immunol 2018; Vol. 28(2): 132-134
doi: 10.18176/jiaci.0220

Key words: Allergy. Delayed hypersensitivity. Lymphocyte transformation test. Sulfadiazine.

Palabras clave: Alergia. Hipersensibilidad tardía. Test de transformación linfocitaria. Sulfadiazina.

Sulfadiazine is an antibiotic from the sulfonamide group that is used to treat toxoplasmosis. Cerebral toxoplasmosis is a highly frequent opportunistic infection of the central nervous system in people with AIDS [1]. The adverse effects of sulfadiazine include hypersensitivity reaction with fever, rash, and pruritus, which may affect up to 30% of persons infected with HIV. It can also cause gastrointestinal complaints, nephrotoxicity, and bone marrow suppression [2] and more common conditions such as nausea, diarrhea, headache, fever, rash, depression, and pancreatitis. Cutaneous reactions to sulfonamides are usually self-limiting and need only symptomatic treatment, although severe reactions can occasionally prove fatal. Mortality is 30%-35% for toxic epidermal necrolysis, 5%-15% for Stevens-Johnson syndrome, and 10% for drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. Cross-reactivity between sulfonamide drugs is controversial [3,4].

We present the case of a 48-year-old woman with a history of hypertension, dyslipidemia, and HIV infection who was coinfected with cerebral toxoplasmosis. She was on treatment with calcium folinate, raltegravir, emtricitabine/tenofovir, hydrochlorothiazide, omeprazole, pyrimethamine, and clindamycin. She was admitted to hospital, where she was diagnosed with cerebral toxoplasmosis and was discharged with levetiracetam, pyrimethamine, sulfadiazine (500 mg, 2 tablets every 6 hours), and trimethoprim-sulfamethoxazole (TMP-SMX) (160 mg/800 mg, 1 tablet 3 times a week). She consulted again 7 days after discharge with an acute 4-day

history of erythematous maculopapular rash on her face, trunk, and upper and lower extremities. Treatment with TMP-SMX was discontinued, but within 72 hours the rash progressed to generalized morbilliform rash accompanied by sensation of fever (temperature not recorded), mild facial edema, and diffuse facial erythema. She was then treated with intravenous dexchlorpheniramine maleate and methylprednisolone and observed at 24 hours. At this time, the patient presented a score of 3 points according to the DRESS diagnostic scale criteria (RegiSCAR) of Kardaun et al [5], indicating a possible case of DRESS. The rash was suggestive of DRESS (exanthema with scaling) and had spread to >50% of the body area. The evaluation of other potential causes (the patient had ≥3 negative viral serology results) added another point to the score. In addition, other data that could support the diagnosis were sensation of fever (temperature not recorded), facial edema, and a rash that lasted for more than 15 days. The patient presented only dubious adenopathy that did not fulfill the criterion for lymphadenopathy (enlargement at 2 or more sites). Similarly, she had no atypical lymphocytes or eosinophilia (maximum count, 290/µL [7%]). However, we must bear in mind that during admission, the patient was receiving dexamethasone, which may have contributed to the fact that she did not present eosinophilia. Liver enzymes were altered, with maximum values of 147 IU/L for aspartate aminotransferase, 261 IU/L for alanine aminotransferase, 370 IU/L for lactate dehydrogenase, and 58 IU/L for gamma-glutamyl transpeptidase at 4 days after admission. Since treatment with sulfadiazine and TMP-SMX was initiated 3 days after the altered liver enzyme values were known, we were able to rule out a potential role of sulfonamides in the alteration. Consequently, the patient met the criteria for DRESS syndrome/exanthema overlap.

Seven days after the onset of rash and associated symptoms, which persisted despite having withheld TMP-SMX, sulfadiazine was replaced by clindamycin, and oral corticosteroids were continued for a week. The skin rash disappeared within a month, with residual dermal scaling. The patient was advised to avoid sulfonamides. Seventeen months after the adverse skin reaction, the patient had CD4 <200 cells/mm^3. She was referred to the allergy unit for assessment of allergy to sulfonamides and desensitization (if necessary), because she needed prophylaxis with TMP-SMX. At that time, the patient's liver enzymes were within the normal range. A skin prick test with sulfadiazine was not performed, because the parenteral presentation was not available in Spain, although the results of a prick test to trimethoprim (10 mg/mL) and prick and intradermal tests to sulfamethoxazole (10 mg/mL) were negative. A late reading of the intradermal test was negative. Patch tests with a standard TRUE-TEST series (Smart Practice Denmark ApS), sulfadiazine, trimethoprim, and sulfamethoxazole [6] were negative. In an attempt to clarify the underlying mechanism, we performed a lymphocyte transformation test (LTT) with sulfadiazine and sulfamethoxazole 19 months after the reaction. Proliferation of lymphocytes was measured as previously described [7]. Briefly, fresh peripheral blood mononuclear cells separated over a density gradient (Histopaque-1077, Sigma-Aldrich) were incubated for 6 days at 10^6 cells/mL in triplicate with sulfadiazine and sulfamethoxazole at concentrations ranging from 10 µg/mL to 200 µg/mL. Phytohemagglutinin (5 µg/mL) was used as a positive control. Proliferation was determined by the addition of [3H]thymidine (0.5 µCi/well) for the final 18 hours of the incubation period. Proliferative responses were calculated as the stimulation index, defined as the ratio between the mean values of counts per minute in cultures with antigen and those obtained without antigen. A positive response, defined as a stimulation index of >2, was obtained with sulfadiazine at all concentrations but not with sulfamethoxazole. The LTT with sulfadiazine and sulfamethoxazole in 3 healthy tolerant individuals revealed no proliferative responses (Table). Given the negative allergy study results with sulfamethoxazole and the need for treatment with this drug, the patient gave her informed consent to undergo an oral tolerance test with increasing doses of TMP-SMX over 3 days until 1 tablet of TMP-SMX (160 mg/800 mg) was tolerated. Laboratory values were monitored and temperature was controlled. Subsequently, the patient continued to take the treatment at home at a dose of 1 tablet every 24 hours for 5 days, thus confirming good tolerance.

We report the case of a patient who developed DRESS/exanthema overlap induced by sulfadiazine. The patient was also treated with sulfamethoxazole, with incomplete criteria for DRESS according to Kardaun et al [5]. As this is a potentially severe reaction and not a simple delayed exanthema, an in vitro test should be performed whenever possible in order to identify the culprit drug and safe alternatives. The implication of

Table. Lymphocyte Transformation Test Results

	Stimulation Index[a]							
	Sulfadiazine, µg/mL				Sulfamethoxazole, µg/mL			
	200	100	50	10	200	100	50	10
Patient	4.9	5.7	3.3	2.1	1.3	0.8	0.9	1.0
Control 1	0.8	0.5	1	0.5	0.5	1.2	1.4	1.0
Control 2	0.8	0.6	0.7	0.9	0.8	0.9	1.0	0.7
Control 3	1.3	1.1	0.8	0.8	0.8	1.1	1.7	1.7

[a]The test is considered positive when the stimulation index is higher than 2 in at least 1 concentration.

sulfadiazine in the reaction was established by a positive LTT result. LTT has a series of advantages over patch and intradermal tests, such as safety and the ability to assess the T-cell response to the drug. In the case we report, LTT was a helpful and safe diagnostic tool for detection of delayed hypersensitivity reaction to sulfadiazine but not to sulfamethoxazole and allowed us to reintroduce sulfamethoxazole safely. To our knowledge, this is the first reported case of hypersensitivity to sulfadiazine in which this drug was shown to be the culprit by a positive LTT result. It has been suggested that there may be a continuous spectrum between maculopapular rash and DRESS [8]. The LTT seems to be a good diagnostic tool for patients who experience delayed reactions to sulfadiazine and sulfamethoxazole, and its usefulness with other drugs has already been demonstrated [9,10]. We did not detect cross-reactivity between sulfadiazine and sulfamethoxazole, which has been well tolerated since the controlled reintroduction of TMP-SMX from June 2016 to October 2017.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received July 23, 2017; accepted for publication December 11, 2017.

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