

# Drug reaction with eosinophilia and systemic symptoms caused by spironolactone: Case report

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**KEYWORDS:** allopurinol, DRESS, spironolactone

Spironolactone is an aldosterone antagonist used as a diuretic and antihypertensive drug.<sup>1</sup> Hypersensitivity reactions to spironolactone are exceedingly rare and usually mild. Only 1 case of a severe cutaneous adverse reaction (SCAR) has been previously reported.<sup>2</sup>

## CASE REPORT

A 79-year-old male with a past history of tophaceous gout (Figure 1A), hypertension and heart failure developed generalized



**FIGURE 1** (A), Clinical presentation of the patient: exuberant tophaceous gout. (B), Diffuse back skin erythema, 6 hours after the intake of a cumulative dose of 38.5 mg of spironolactone during a drug provocation test. (C), Positive patch test results with the 100-mg spironolactone tablet: 1, 25 mg/mL saline; 2, 5 mg/mL saline; 3, 2.5 mg/mL saline; 4, 0.25 mg/mL saline; 9, 50% pet.; 10, 20% pet.; 11, 10% pet.; 12, 1% pet. Patch tests with allopurinol: 5–8, respectively 50, 10, 7.5 and 0.5 mg/mL saline; and 13–16, respectively 1 50-mg tablet prepared in pet. at 50%, 20%, 10%, and 1%

pruritic exanthema 10 days after he started taking amlodipine 5 mg, spironolactone 100 mg and allopurinol 300 mg. He was seen in the emergency department, and advised to stop taking all new medications. In the following 6 days, the skin eruption continued with increasing pruritus; he was febrile (39 °C) and progressively developed facial oedema and erythema, pharyngeal tightening, enlarged lymph nodes, and confusion. Laboratory work-up showed leukocytosis ( $20.8 \times 10^9/L$ ), hypereosinophilia (40.9%,  $8500/mm^3$ ), alanine transaminase 84 U/L, aspartate transaminase 69 U/L, Alkaline phosphatase 261 U/L, and  $\gamma$ -glutamyl transferase 204 U/L, fulfilling the RegiSCAR criteria for possible drug reaction with eosinophilia and systemic symptoms (DRESS). He was hospitalized, all remaining medications were stopped, and oral prednisone 1 mg/kg daily was started. His symptoms gradually improved, and the rash resolved within 12 days. Lifelong avoidance of allopurinol, amlodipine and spironolactone was recommended.

Seven years after this episode, the patient was referred to our Drug Allergy Consultation to confirm hypersensitivity to allopurinol, which was highly needed for the treatment of his gout. Taking into consideration that oral challenge is not advised in patients with SCAR and allopurinol is among the most frequent causes of DRESS,<sup>3</sup> whereas only 1 case report has associated DRESS with spironolactone<sup>2</sup>, and another has associated it with amlodipine/perindopril,<sup>4</sup> a diagnostic drug provocation test was planned, initially with oral spironolactone. He tolerated 10 mg, 10% of the dose, without immediate symptoms, but, on the second day, 6 hours after the second dose (28.5 mg), he developed generalized skin erythema (Figure 1B) and pruritus, without fever. He had hypereosinophilia (30%,  $2.5 \times 10^9/L$ ), but no other blood count or liver function alterations. Methylprednisolone (125 mg intravenous) was administered, and symptoms resolved within 12 hours. No further DPTs were performed.

Six weeks later, epicutaneous patch tests with spironolactone and allopurinol were performed. Drug tablets containing 100 mg of spironolactone and 300 mg of allopurinol were crushed, prepared in pet. or saline solution in decreasing dilutions, at concentrations known to be non-irritant<sup>5</sup>, and applied on the upper back for 2 days with Finn Chambers (SmartPractice, Phoenix, Arizona) on Scanpor tape (Norgesplaster, Vennessla, Norway). A strong (++) positive reaction was observed only to spironolactone on day 2 at all tested concentrations and vehicles (up to 1% pet. and 0.25 mg/mL of saline) (Figure 1C), whereas allopurinol tests gave negative results.

Lymphocyte transformation tests (LTT) performed with spironolactone and allopurinol 100mg to 1pg, 1/10 serial dilutions, were negative. HLA class I/II typing identified HLA-A\*01,\*02; HLA-B\*13, \*53; HLA-C\*06, \*07; DRB1\*07,\*13; DQA1\*01, \*01; DQB1\*02,\*06.

## DISCUSSION

Reports of delayed hypersensitivity reactions to spironolactone are very scarce: contact dermatitis was described in 3 patients,<sup>1</sup> and only 1 case report associated spironolactone with DRESS.<sup>2</sup> In this patient, a positive drug provocation test result with rash and hypereosinophilia, and positive patch test results, support spironolactone as the culprit in DRESS, even though LTTs failed to confirm these results.

Patch testing with spironolactone has been used to identify sensitization in both contact dermatitis and DRESS.<sup>1</sup> In our patient, both saline and pet. preparations produced unequivocally positive reactions, even at low concentrations (Figure 1C). These findings support the use of patch testing as a standardized methodology to study delayed hypersensitivity reactions to spironolactone, and it should be used before drug provocation tests in patients with SCARs. On the other hand, a LTT failed to identify hypersensitivity. The metabolism of spironolactone and antigenic recognition by T cells are unknown, and an in vitro method may not allow the formation of the relevant antigenic epitope for T cell stimulation.

## Conflict of interest

The authors declare no potential conflict of interests.

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**How to cite this article:** Fernandes R-A, Regateiro FS, Faria E, Martinho A, Gonçalo M, Todo-Bom A. Drug reaction with eosinophilia and systemic symptoms caused by spironolactone: Case report. *Contact Dermatitis*. 2018;79:255-256. <https://doi.org/10.1111/cod.13073>