## Allopurinol-Induced DRESS and Neosensitization to Thalidomide: Complex Management and Diagnosis in a Patient With Multiple Myeloma

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, complex, potentially life-threatening, drug-induced hypersensitivity reaction that is considered to be a severe cutaneous adverse reaction (SCAR) to drugs. It is characterized by skin eruption, hematologic abnormalities, lymphadenopathy, and internal organ involvement [1].

We report the case of a 51-year-old woman with a history of recurrent depressive disorder and IgG kappa multiple myeloma. She had recently started chemotherapy with bortezomib, thalidomide, and dexamethasone plus prophylaxis with allopurinol, acyclovir, bemiparin, zoledronic acid, famotidine, and olanzapine (for a corticosteroid-related hypomanic episode).

She presented at the emergency department with intensely pruritic exanthema consisting of erythematous papules mainly affecting the trunk, external aspects of the limbs, and dorsal surfaces of hands and feet (Supplementary Figure 1). The initial differential diagnosis included viral rash and chemotherapy-related toxicoderma. A skin biopsy was performed, and prednisone was started.

Despite administration of a corticosteroid, her skin condition worsened over the following 2 days, and mild erosive lesions appeared on the buccal mucosa. Blood tests revealed eosinophilia (1040/µL), and histopathology revealed marked lymphocytic and eosinophilic infiltrates in the dermis and spongiosis. Thalidomide was discontinued owing to the suspicion of a SCAR. However, the morphology of the cutaneous eruption changed 48 hours later to dusky, targetoid lesions (Supplementary Figure 2), necessitating a second biopsy. Although the Nikolsky sign was negative, oral involvement and atypical target lesions, together with pathological changes and blood eosinophilia, suggested overlapping DRESS and Stevens-Johnson syndrome (SJS). The patient was admitted to hospital for multidisciplinary management and treated with intravenous methylprednisolone 60 mg. Although her skin rash improved on the trunk and extremities, she developed facial edema (mainly periorbital), worsening of eosinophilia (2470/µL), and slight liver damage (Supplementary Figure 3). Considering her previous psychiatric reaction to corticosteroids and the absence of resolution at that dose, we decided to switch treatment to etanercept 50 mg based on the hybrid characteristics of the drug reaction and previous reports showing the benefit of tumor necrosis factor α (TNF-α) inhibitor therapy both in SJS and DRESS [2-6]. Facial involvement, rash, and eosinophilia started to resolve within the following 48 hours. A second dose of etanercept 25 mg was administered 3 days after the first injection. Complete clearance was achieved 5 days after the first dose, and the patient was discharged. She received a course of oral prednisone with gradual tapering.

SJS and toxic epidermal necrolysis (TEN) overlap was ruled out by the second biopsy (Supplementary Figure 4). Negative results were recorded in ANA testing, blood culture, and serology testing for *Chlamydia*, *Mycoplasma pneumoniae*, arbovirus B19, HHV-6, CMV, EBV, HAV, HBV, HCV, and HIV. Reactivation of HHV-6 was detected 48 days after the onset of skin rash.

Although the patient progressed favorably, several flares of papular skin lesions coincided with tapering of oral corticosteroids and administration of topical corticosteroids, topical tacrolimus, cyclosporine, and prednisone. The patient was referred to the allergy department after discharge. We took a detailed clinical history and a prepared a timeline chart to bring together signs and symptoms, time of onset and resolution, and all the drugs taken whose latency period was compatible with DRESS syndrome (Supplementary Figure 3).

Applying the Spanish Pharmacovigilance System Algorithm [7], we found possible causality [+5] for bortezomib and famotidine and probable causality [+6] for thalidomide, allopurinol, and olanzapine.

A lymphocyte transformation test (LTT) [8] revealed a negative result with famotidine and olanzapine and a positive result with oxypurinol at all concentrations tested (stimulation index [SI] of 2.7, 6.35, 13.2, and 24.39). However, the result with bortezomib and thalidomide was doubtful, with a slightly positive value at only 1 concentration (SI of 2.01 and 2.13, respectively).

The hematologist recommended bortezomib and thalidomide as first-line treatment. The patient gave her written informed consent for gradual controlled challenge tests after weighing up the risks and benefits. These were performed with clinical and laboratory monitoring according to the Spanish Guidelines for Management of DRESS [9]. Bortezomib 1.25 mg and thalidomide 25 mg and 50 mg were well tolerated. The diagnosis was probable DRESS

 

(RegiSCAR score 5) induced by allopurinol (Supplementary material).

Seventeen days after the reintroduction of both drugs, the patient returned to the emergency department with a confluent erythematous maculopapular rash on her trunk and limbs that was associated with an increase in the dose of thalidomide (from 100 mg/d to 150 mg/d) 3 days before (Supplementary Figure 5). The diagnosis was drug eruption with neosensitization to thalidomide. This drug was suspended, and prednisone 30 mg was prescribed. We decided to perform a desensitization protocol with thalidomide [10]. Desensitization was finally achieved after 44 days and under premedication with anti-H1 and prednisone 10 mg. The patient was able to complete treatment with bortezomib and thalidomide prescribed by the hematologist before stem cell transplantation.

Although the pathogenesis of DRESS remains speculative [1], potential mechanisms include a T cell–mediated hypersensitivity reaction in which the immune response is elicited by specific drugs and reactivation of human herpesvirus.

Treatment remains challenging, and relapses are frequent. TNF-α appears to be significantly involved in tissue damage in the setting of SCARs. Rapid resolution of skin lesions in TEN after treatment with TNF-α inhibitors has been widely reported and supports this hypothesis [2]. Conversely, the few cases of DRESS that have been managed with this approach [5,6] point to promising results in the treatment of skin and liver damage.

In the case we report, the onset of skin symptoms after discontinuation of bortezomib and thalidomide led us to hypothesize that the immunomodulatory effect of these drugs delayed the condition caused by allopurinol. Thalidomide might enhance or inhibit the production of TNF-α, enhance cytokine production and the cytotoxic activity of T cells and NK cells, and act as a low-molecular-weight xenobiotic, possibly leading the patient to develop drug-specific T cells.

The presence of multiple drugs and confounding dermatologic features suggesting overlapping DRESS and SJS complicated the diagnosis. A TNF-α blocker was a reasonable therapeutic alternative, especially considering the lack of response and contraindication to increasing the corticosteroid dose.

As a diagnostic tool, LTT proved useful for identifying allopurinol as the culprit drug. It enabled a safe, controlled exposure test with the other drugs involved based on the Spanish DRESS guidelines [9]. Neosensitization to thalidomide necessitated a desensitization protocol, which enabled the patient to be treated with first-line therapy.

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*Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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