Allopurinol induced - DRESS and neo-sensitization 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, characterized by skin eruption, hematologic abnormalities, lymphadenopathy and internal organ involvement [1].

Our patient is a 51-year-old woman with 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 to the emergency room with an intensely pruritic exanthema consisting of erythematous papules mainly affecting trunk, external aspects of limbs and dorsal surfaces of hands and feet (Figure 1). Initial differential diagnosis included viral rash and chemotherapy-related toxicoderma. A skin biopsy was performed and prednisone was started.

Despite corticosteroid treatment, skin worsened in the following two days and mild erosive lesions appeared in jugal mucosa. Blood tests revealed eosinophilia (1040 cells/µL), and pathological results showed marked dermal infiltrates of lymphocytes and eosinophils and spongiosis. Under suspicion of a SCAR, thalidomide was discontinued.

However, morphology of the cutaneous eruption changed 48 hours later to dusky, targetoid lesions (Figure 2), requiring a second biopsy. Although Nikolsky’s sign was negative, oral involvement and atypical target lesions together with pathological changes and blood eosinophilia suggested DRESS- Stevens-Johnson Syndrome (SJS)

Key words: DRESS syndrome. Drug reaction with eosinophilia and systemic symptoms. Lymphocyte transformation test. Etanercept. Allopurinol.

Palabras clave: Síndrome DRESS. Reacción adversa a fármaco con eosinofilia y sintomatología sistémica. Test de transformación linfocitaria. Etanercept. Alopurinol.
overlap. The patient was admitted to hospital for multidisciplinary management, and treated with 60mg intravenous methylprednisolone. Although skin rash improved in trunk and extremities, she developed facial edema mainly periorbital, worsening of eosinophilia (2470 cells/µL) and slight liver damage (Figure 3). Considering her precedent psychiatric reaction with corticosteroids and absence of resolution on that dose, we decided to switch treatment to etanercept 50mg based on the hybrid characteristics of the drug reaction and the previous reports showing benefit of tumor necrosis factor alfa (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 25 mg of etanercept was administered three 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/TEN was ruled out by the second biopsy (Figure 4). ANA, blood culture and serologies for Chlamydia and Mycoplasma pneumoniae, Parvovirus B19, HHV-6, CMV, EBV, HAB, HBV, HCV and HIV were negative. HHV-6 reactivation was detected 48 days after the onset of skin rash. Although evolution was favourable, several flares of papular skin lesions appeared coinciding with tapering of oral steroids, managed with topical steroids, topical tacrolimus, ciclosporin and prednisone. The patient was referred to allergy department after discharge. We conducted a detailed clinical history and a timeline chart to bring together signs and symptoms, time of onset and resolution, and all of the drugs taken with a latency period compatible with DRESS syndrome (Figure 3).


A lymphocyte transformation test (LTT) [8] revealed a negative result with famotidine and olanzapine and a positive result with oxypurinol at all the concentrations tested (stimulation indeces (SI) of 2.7, 6.35, 13.2, 24.39). However, it was doubtful with
bortezomib and thalidomide, with a slight positivity just at one 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 considering risks and benefits. They were performed with clinical and laboratory monitoring according to the Spanish Guidelines for Management of DRESS [9]. Bortezomib 1.25mg and thalidomide 25mg and 50mg, were administered with good tolerance. The diagnosis was probable DRESS (RegiSCAR score 5) due to allopurinol (Supplementary material).

17 days after the reintroduction of both drugs, the patient returned to the emergency room with a confluent erythematous maculopapular rash in her trunk and limbs that related to an increase in the dose of thalidomide (from 100mg to 150mg a day) 3 days before (Figure 5). Drug eruption with neo-sensitization to thalidomide was diagnosed. This drug was suspended and prednisone 30mg was prescribed. Thalidomide administration was decided following a desensitization regimen [10]. This was finally obtained after 44 days and also under premedication with anti-H1 and prednisone 10 mg. The patient could complete treatment with bortezomib and thalidomide prescribed by the hematologist before hematopoietic transplantation.

Although the pathogenesis of DRESS remains speculative [1] a T-cell mediated hypersensitivity reaction in which immune response is elicited by specific drugs and a chained viral reactivation involving human herpesviruses seem to play a crucial role.

Treatment remains a challenge 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 TNF-α inhibitors treatment has been widely reported and support this hypothesis [2]; conversely, only few cases of DRESS have undergone such therapy [5,6], with promising results in skin and liver damage improvement.

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

The presence of multiple drugs and confounding dermatologic features suggesting DRESS/SJS overlap made the diagnosis complicated. TNF-α blocker represented a reasonable therapeutic alternative, especially considering lack of response and contraindication to increase steroid dose.

LTT was a useful diagnostic tool identifying allopurinol as the culprit drug. It allowed a safe controlled exposure test with the other involved drugs based on the Spanish DRESS guidelines [9]. Neo-sensitization to thalidomide required an eventual desensitization regimen and finally our patient could be treated with first-line therapy.

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The authors declare that they have no conflicts of interests to disclose.
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FIGURES

Figure 1. Initial lesions.
Figure 2. Skin lesions 48 hours after thalidomide withdrawal.
Figure 3. Timeline chart with signs, symptoms, time of onset and resolution, and drugs taken with a latency period compatible with DRESS syndrome.
Figure 4. Exanthema after reintroduction of thalidomide.

Superficial perivascular lymphocytic infiltrate, with numerous interstitial eosinophils, and vacuolar alteration of the dermoepidermal junction. In the epidermis there are practically no necrotic keratinocytes.

Diagnosis: Dermatitis of the vacuolar interface, with numerous eosinophils.

Note: The most likely diagnosis is toxicoderma, although this lesion is not toxic epidermal necrolysis.
Figure 5. Skin biopsy performed on day 8.