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Successful desensitization procedure to lenalidomide in a patient with delayed hypersensitivity confirmed with a positive LTT

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Clinical implications: we presented the case of a short successful desensitization procedure to lenalidomide in a patient with delayed hypersensitivity confirmed with a positive LTT

To the editor:

Lenalidomide is an immunomodulatory oral synthetic-derivative of thalidomide which is indicated in association with dexamethasone in refractory multiple myeloma (MM) and when it relapses. Lenalidomide acts inducing apoptosis of tumour cells and changes in micro-environmental conditions of tumour stroma and angiogenesis, and stimulating the host immune response through the activation of cytotoxic T-lymphocytes and Natural Killer-cells [1,2].

Adverse drug reactions (ADRs) to lenalidomide range from 6% to 43%, mostly morbilliform, urticarial and maculopapular exanthema occurring within the first month of treatment [3]. Some cases of severe cutaneous ADRs have also been reported such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). According to a meta-analysis conducted on ten trials, the overall incidence of all-grade and high-grade rash was 27.2% and 3.6%, respectively [4]. In most cases, the relationship between the drug and rash development was suggestive leading to the removal of the drug, but they could not be ascertained with an objective test.

We present the case of a 77-year-old man with MM (lambda-light-chain disease, stage Durie Salmon IIIB, ISS3) diagnosed 2 years before, with renal impairment and bone lesions. His personal background included a colostomy for diverticulitis, inguinal herniorraphy and a transurethral resection for prostatic hypertrophy. He presented a previous allergic reaction to colistin, but he had no history of either food or latex allergy, rhinitis or asthma. A third-line treatment with lenalidomide (10 mg/24h on days 1 to 21 of a 28-day cycle)-dexamethasone was initiated in February 2017 upon evidence of disease progression. In December 2017, after 5 days on the 10th cycle, he experienced an acute pruritic exanthema, developing a generalized morbilliform eruption on the trunk and folds with residual flaking skin. No mucosa involvement was observed. Neither pustules, vesicles or blisters were present. No eosinophilia, enlarged lymph nodes,

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elevated creatinine or hepatitis signs were detected. With the suspicion of a toxicodermic reaction, the discontinuation of lenalidomide was decided and the patient was treated with oral prednisolone for two weeks.

In an attempt to clarify the underlying mechanism of this reaction, a lymphocyte transformation test (LTT) with lenalidomide was performed. This method is performed by incubating fresh peripheral-blood mononuclear cells from patient previously separated over a density gradient (Histopaque-1077, Sigma-Aldrich) for 6 days at 10^6 cells/mL, at different concentration of the suspected drug. In this case, the test was performed in triplicates with lenalidomide at 0.1 μg/mL-100μg/mL. Drug was provided by the Hospital Pharmacy. Phytohemagglutinin (5 μg/mL) was used as positive control. Proliferation was determined by the addition of [^{3}H]thymidine (0.5 μCi/well) for the final 18 hours of the incubation period. The result is expressed as stimulation index (SI), which is the relationship between proliferation of lymphocytes in the presence or absence of the drug (basal proliferation). A positive result is suggestive of sensitization to the drug although a negative result does not exclude sensitization [5]. The positive control result was 181 counts per minute (cpm) and that of basal proliferation was 58 cpm. A positive response, defined as an SI of over 2 in at least one of the doses tested, was obtained with lenalidomide. LTT with lenalidomide in 3 different healthy controls showed no proliferative responses (Fig. 1).

A progression of the disease was verified in May 2018 and the haematologist decided to reintroduce the drug as the treatment of choice. Different strategies have been suggested for hypersensitivity dermatologic reactions induced by lenalidomide, including drug discontinuation or antihistamine and corticosteroid premedication. There are some few published reports of rapid inpatient desensitization in patients with acute urticarial rash [6] and an outpatient 6-week desensitization protocol for a target dose of 10 mg, in 5 patients with cutaneous delayed reaction [7]. Considering the presence of an immunological mechanism causing the reaction and assessing all possible treatment options, we decided to perform a desensitization procedure. After assessing the safety of drug handling for small doses, a first attempt was initiated with a dose escalation procedure, rising daily the dose from 1 mg, which was planned to last 5 days (1, 2, 2.5, 5, 10 mg). Under specialist supervision in our outpatient clinic, the heart rate, blood pressure, pulse oximetry and peak-flow rate were monitored. This first attempt was

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interrupted at the third day of treatment, four hours later to the drug intake, the patient reported the presence of an intense armpits and scalp itching in absence of skin lesions, which persisted 48 hours after the removal of the drug. Cutaneous symptoms were accompanied by a single and self-limited episode of diarrhoea. Since the first attempted desensitization protocol failed, we designed a new one with dose escalation every 2 days based on previous recommendations in delayed reactions to allopurinol [3]. We also restarted the procedure from a lower initial dose, adding concomitant bilastine 20 mg/24 h. Table I shows the adjusted 14-day protocol that was carried out from the initial dose of 0.1 mg of lenalidomide up to 10 mg/24h according to the dose prescribed by the hematologist. Escalating doses were tolerated, achieving the dose of 10 mg, since he continued to receive this daily dose of 10 mg for the next two months, without appearance of new episodes of itching, diarrhoea, or skin involvement.

We report the case of a patient who developed a delayed erythematous morbilliform skin eruption in course of taking lenalidomide. For the first time, the implication of this drug was established by a positive LTT. Although LTT has not been completely standardized yet for many drugs, it should be considered a useful *in vitro* diagnostic tool, especially in non-immediate reactions. LTT reflects the reactivation and proliferation of memory cells that are present in the peripheral blood of allergic patients and it is not necessarily associated with more severe clinical symptoms and a dose-response pattern [9]. For some drugs, LTT could offer a better diagnostic value than patch and intradermal tests to identify allergic subjects [10, 11]. For drugs such as beta-lactams, LTT can reach a 92.8% of specificity, obtaining positive results even 10 or more years after the occurrence of the reaction, without further exposure to the drug [12]. Moreover, LTT is safe for patients, which is absolutely relevant for severe reactions. In addition, we could propose an effective and safe alternative with a 14-day desensitization procedure, although it needs to be further validated in more patients.

In summary, this is the first reported case of a patient with hypersensitivity to lenalidomide, demonstrated by a positive LTT, in whom a short successful outpatient oral desensitization procedure was performed.

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