

---

## Successful Desensitization to Lenalidomide in Leukocytoclastic Vasculitis

---

Fernández-Concha I<sup>1</sup>, Pose K<sup>1</sup>, de las Vecillas L<sup>1,2</sup>, Lluch-Bernal M<sup>1,2</sup>, Tomás-Pérez M<sup>1,2</sup>, Soto T<sup>2,3</sup>, López de la Guía A<sup>2,3</sup>, Cabañas R<sup>1,2,4,5</sup>

<sup>1</sup>Allergy Department, Hospital Universitario La Paz, Madrid, Spain  
<sup>2</sup>Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

<sup>3</sup>Hematology Department, Hospital Universitario La Paz, Madrid, Spain

<sup>4</sup>PIELenRed consortium

<sup>5</sup>Center for Biomedical Re-search Network on Rare Diseases (CIBERER U754), Madrid, Spain

---

J Investig Allergol Clin Immunol 2024; Vol. 34(5):  
doi: 10.18176/jiaci.1002

---

**Key words:** Leukocytoclastic vasculitis. Desensitization protocol. Lenalidomide. Multiple myeloma.

**Palabras clave:** Vasculitis leucocitoclástica. Protocolo de desensibilización. Lenalidomida. Mieloma múltiple.

---

Multiple myeloma (MM) is an incurable disease that can be treated effectively with multiple therapy lines. Lenalidomide is one of the standard treatments for MM and is taken in combination with dexamethasone or other drugs, either as first-line therapy or as rescue treatment [1]. Leukocytoclastic vasculitis (LV) is a cutaneous, small-vessel vasculitis of the dermal capillaries and venules that is clinically characterized by the presence of palpable purpura and/or petechiae. Histopathologically, it is characterized by the deposition of immune complex on the walls of small vessels.

LV has rarely been reported in association with MM and is more commonly associated with immunoglobulin A (IgA) myeloma. Drugs are the most identified cause in these cases. Drug-induced vasculitis is a poorly defined disorder, and establishing causality can be difficult. Onset typically occurs 1 to 3 weeks after initiation of therapy and is often induced by  $\beta$ -lactams, erythromycin, clindamycin, vancomycin, sulfonamides, furosemide, allopurinol, and nonsteroidal anti-inflammatory drugs, among others [2]. The literature contains 1 case report with lenalidomide [3] and 3 with thalidomide [4-6].

Information on desensitization in drug-induced LV is scarce, except for a single case report with methotrexate [7]. However, there is evidence of successful desensitization with additional corticosteroids in serum sickness-like reaction (also an immune complex-mediated hypersensitivity disease) due to rituximab [8,9].

We present the case of an 82-year-old woman initially diagnosed with IgA $\lambda$  monoclonal gammopathy of uncertain significance in January 2017. This progressed to symptomatic MM ISS 3 in October 2018 (compression fracture of D12, anemia, hypercalcemia, and renal impairment).

The patient started lenalidomide 25 mg daily and dexamethasone 40 mg once a week. On the third and fourth days of taking lenalidomide 25 mg, she presented with significant asthenia, uncontrollable back pain, and purpuric lesions: plaques formed by minute palpable punctiform papules with a central hemorrhagic scar, which extended from the knee to the back of both feet, and a few lesions on her thighs. No edema, arthralgia, fever, or other associated symptoms were present.

The blood and urine work-up did not indicate systemic involvement, and the values of antineutrophilic cytoplasmic antibodies (anti-MPO and anti-PR3) were negative. The Spanish Pharmacovigilance System causality algorithm showed that causality was conditional (+3) for lenalidomide, which was discontinued. Biopsy results later confirmed LV (image 1 [Supplementary online material]). The patient was successfully treated with systemic and topical corticosteroids, and her symptoms resolved.

Treatment was switched to bortezomib, melphalan, and prednisone, leading to a complete response by November 2019. The patient relapsed in April 2021; therefore, treatment with daratumumab, bortezomib, and dexamethasone was started, leading to a partial response after 18 cycles. In October 2022, she relapsed again. Given the patient's age and previous treatments received, it was decided to start rescue treatment with lenalidomide.

Recognizing the urgent need for this drug and following a thorough risk-benefit assessment by the allergy team and hematologists, a desensitization protocol was proposed to reintroduce the treatment after obtaining the patient's informed consent.

We used a lenalidomide desensitization protocol designed by our group and previously published [10] after adapting it to the target dose and the initial reaction.

Desensitization started at 0.1 mg of lenalidomide with a target dose of 15 mg and ebastine 20 mg as premedication. The desensitization process encountered unexpected challenges. The patient tolerated daily doses of 0.1 mg, 0.5 mg, 1 mg, 2.5 mg, and 5 mg. However, with the second and third doses of 5 mg, she developed pruritus and erythema on the scalp, ears, and neck. This required treatment with 40 mg IV of methylprednisolone and a reduction of lenalidomide to 2.5 mg plus prednisone 10 mg for 1 day to resolve the symptoms. Then, prednisone was reduced to 5 mg/d, while lenalidomide remained at 2.5 mg. Despite the reduction in the dose of the culprit drug, purpuric lesions developed on the lower limbs between days 10 and 16. Subsequently, prednisone was

increased to 10 mg, and lenalidomide was continued at 2.5 mg for 5 days. The lesions disappeared. Therefore, on day 22, the lenalidomide dosage was increased to 5 mg/d and maintained for 1 week, while prednisone was maintained at 10 mg/d, along with ebastine 20 mg. On day 29, lenalidomide was increased to 7.5 mg/d for 1 week, and, given that the patient tolerated the drug well, a dose of 10 mg was reached on day 39.

Owing to the breakthrough reactions during desensitization, the hematologists decided to change the target dosage of lenalidomide to 10 mg/d in a continuous regimen, rather than following the original protocol of 15 mg for 21 days followed by a 7-day rest. The prednisone dose was gradually tapered and eventually discontinued on day 55. Following the reintroduction of lenalidomide, MM was controlled and the patient's symptoms stabilized.

In February 2023, the patient developed pneumonia owing to influenza B, and lenalidomide was suspended. The desensitization protocol was initiated once again, this time with ebastine 20 mg and prednisone 10 mg from baseline. Desensitization started with 0.1 mg of lenalidomide on day 1, 0.5 mg on day 2, and 1 mg on day 3. From day 4 to day 10, she received 2.5 mg daily; between days 11 and 17, she received 5 mg; and between days 18 and 24, she received 7.5 mg. On day 25, the target dose of 10 mg was achieved and tolerated. The prednisone dose was slowly reduced until it was completely discontinued. At present, the patient is taking 10 mg of lenalidomide daily plus ebastine 20 mg, without concomitant corticosteroids, and her MM remains in clinical remission.

Both drugs and hematological diseases can cause LV. Initially, it was challenging to conclusively attribute the LV to lenalidomide rather than MM, particularly owing to the rapid onset of symptoms. However, when the lesions reappeared upon reintroduction of lenalidomide during desensitization, the suspicion was confirmed.

We present the outcome of a successful lenalidomide desensitization protocol in a patient with lenalidomide-induced LV and no other therapeutic options. Premedication with corticosteroids was necessary to ensure the success of desensitization, as previously recommended in other cases of desensitization when a type III hypersensitivity reaction is suspected [7-9]. This is the first reported protocol for lenalidomide-induced LV and for any other oral drug-induced LV. We wish to emphasize the importance of desensitization for first-line treatments and its positive impact on the prognosis of life-threatening disease.

#### 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.

#### Previous Presentations

This case was presented as a poster at the 10th EAACI Drug Hypersensitivity Meeting (DHM).

#### References

1. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2022;97:1086-107.
2. Fraticelli P, Benfaremo D, Gabrielli A. Diagnosis and management of leukocytoclastic vasculitis. *Intern Emerg Med.* 2021;16:831-41.
3. Loree JM, Cai E, Sheffield BS, Dutz JP, Villa D, Shepherd LE, et al. Leukocytoclastic vasculitis following lenalidomide during the treatment of follicular lymphoma. *Leuk Lymphoma.* 2017;58:711-4.
4. Cem Ar M, Soysal T, Hatemi G, Salihoglu A, Yazici H, Ulku B. Successful management of cryoglobulinemia-induced leukocytoclastic vasculitis with thalidomide in a patient with multiple myeloma. *Ann Hematol.* 2005;84:609-13.
5. Yildirim ND, Ayer M, Kucukkaya RD, Alpay N, Mete O, Yenerel MN, et al. Leukocytoclastic Vasculitis due to Thalidomide in Multiple Myeloma. *Jpn J Clin Oncol.* 2007;37:704-7.
6. Montefusco V, Galli M, Spina F, Stefanoni P, Mussetti A, Perrone G, et al. Autoimmune diseases during treatment with immunomodulatory drugs in multiple myeloma: selective occurrence after lenalidomide. *Leuk Lymphoma.* 2014;55:2032-7.
7. Hanna C, Villa D, Irani C, Ghosn M, El Rassy E. Leukocytoclastic Vasculitis and Desensitization to High-dose Methotrexate in Primary Central Nervous System Lymphoma. *Clin Lymphoma Myeloma Leuk.* 2018;18:197-200.
8. Fajt M, Petrov A. Desensitization Protocol for Rituximab-Induced Serum Sickness. *Curr Drug Saf.* 2014;9:240-2.
9. Wong JT, Long A. Rituximab Hypersensitivity: Evaluation, Desensitization, and Potential Mechanisms. *J Allergy Clin Immunol Pract.* 2017;5:1564-71.
10. Pose K, Narváez-Fernández E, López de la Guía A, De Las Vecillas L, Domínguez-Ortega J, Lluch-Bernal M, et al. A tailored 7- to 10-day lenalidomide desensitization protocol. *J Investig Allergol Clin Immunol.* 2024;34(1):49-50.

■ Manuscript received January 30, 2024; accepted for publication March 6, 2024.

**Ines Fernandez Concha**

Department of Allergy  
La Paz University Hospital  
Madrid, Spain

E-mail: ifconchallona@salud.madrid.org