References

1. Zouboulis CC, Bechara FG, Dickinson-Blok JL, Gulliver W, Horváth B, Hughes R, et al. Hidradenitis suppurativa/acne inversa: A practical framework for treatment optimization–systematic review and recommendations from the HS ALLIANCE working group. J Eur Acad Dermatol Venereol. 2019;33:19–31.
2. Martorell A, García FJ, Jiménez-Gallo D, Pascual JC, Pereyra-Rodríguez J, Salgado L, et al. Update on hidradenitis suppurative (Part II): Treatment. Actas Dermosifiliogr. 2015;106:716–24.
3. Weber P, Seyed Jafari SM, Yawalkar N, Hunger RE. Apremilast in the treatment of moderate to severe hidradenitis suppurativa: A case series of 9 patients. J Am Acad Dermatol. 2017;76:1189–91.
4. Vossen ARJV, van Doorn MBA, van der Zee HH, Prens EP. Apremilast for moderate hidradenitis suppurativa: Results of a randomized controlled trial. J Am Acad Dermatol. 2019;80:80–8.
5. Kerdel FR, Azevedo FA, Kerdel Don C, Don FA, Fabbrocini G, Kerdel FA. Apremilast for the treatment of mild-to-moderate hidradenitis suppurativa in a prospective, open-label phase 2 study. J Drugs Dermatol JDD. 2019;18:170–6.
6. Lanna C, Mazzilli S, Zangrilli A, Bianchi L, Campione E. One drug and two diseases: A case of multidrug-resistant hidradenitis suppurativa and psoriasis treated with apremilast. Dermatol Ther. 2019;32:e13089.

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Leflunomide-Induced Phototoxic Reaction in a Woman With Systemic Lupus Erythematosus☆

Erupción fototóxica inducida por leflunomida en una paciente con lupus eritematoso sistémico

To the Editor:

Leflunomide is an immunosuppressive agent that has been approved by the United States Food and Drug Administration for the treatment of rheumatoid arthritis and psoriatic arthritis. It is also widely used off-label in other diseases, such as ankylosing spondylitis and systemic lupus erythematosus (SLE). Leflunomide can produce adverse effects, the most common of which are gastrointestinal symptoms, hypertension, and alopecia. Although considered an efficacious and safe drug for the treatment of SLE, leflunomide has been associated with cases of skin rash, such as erythema multiforme[1], toxic epidermal necrolysis[2], and vasculitis[3], and it has even triggered skin lesions in subacute lupus erythematosus[4].

A 25-year-old woman had been followed by the rheumatology department for a 4-year history of SLE. The diagnostic criteria did not include a history of photosensitivity. Initial treatment was with rituximab (500 mg every 15 days, 2 sessions), oral prednisone in tapering doses, and subcutaneous methotrexate (17.5 mg weekly). Owing to gastrointestinal adverse effects, methotrexate was replaced by leflunomide (3 daily doses of 100 mg followed by a maintenance dose of 20 mg/d) 3 months after initiation. Two months after starting treatment with leflunomide and after intense exposure to sunlight at the beach, the patient came to the clinic with a 24 -h history of very pruritic generalized maculopapular rash (Fig. 1A-B), which progressed to vesicular-bullous lesions in 48 hours. These mainly affected the arms (Fig. 1C) and were associated with pustules on the forehead (Fig. 2A), vesicles on the area of the lips (Fig. 2B), and ecchymotic macules and papules on both axillae (Fig. 2C). Examination of the oral and genital mucosa was normal. The laboratory workup revealed high titers for antinuclear antibodies (1/640 U/mL), anti-Ro/SSA-60 (157), anti-Ro/SSA-52 (167), and rheumatoid factor (80 U/mL). Values for the remaining parameters, including C3 and C4, were normal. Serology testing (herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6) yielded negative results. Histopathology of a punch biopsy specimen from a bullous lesion on the posterior trunk revealed an atrophied epidermis with foci of necrotic keratinocytes and spongiosis, together with a subepidermal bullous formation and a moderate inflammatory perivascular mononuclear infiltrate of lymphocytes and eosinophils in the dermis that was compatible with phototoxic rash. Direct immunofluorescence was negative. Treatment with leflunomide was interrupted, and systemic treatment with oral prednisone (1 mg/kg/d) was started. The lesions had resolved completely after 10 days except for some residual hyperpigmentation.

Patients with SLE are particularly sensitive to sunlight, which is considered a trigger or aggravating factor of the disease. It is rare for a diagnosis of SLE not to include photosensitivity as a criterion. Of the various treatments used in SLE, leflunomide is not a first choice; therefore, it is used in selected patients who experience adverse effects associated with other drugs, such as methotrexate. The literature contains many articles that consider leflunomide as the sole cause of subacute cutaneous lupus erythematosus (SCLE)[5], as well as SCLE associated with erythema multiforme–type lesions and erythema multiforme major. Some authors are in favor of diagnosing the co-occurrence of lupus erythematosus and erythema multiforme in the same patient as Rowell

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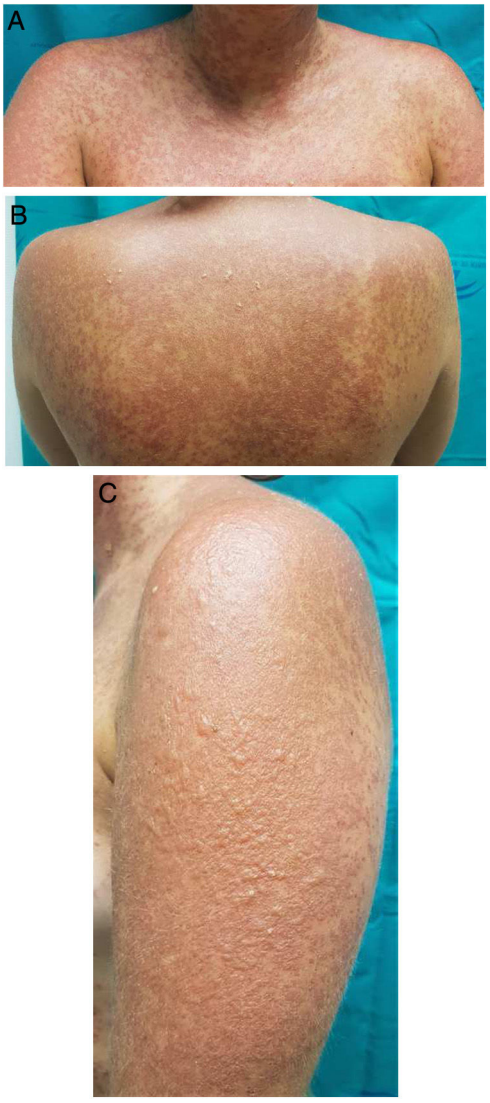

Figure 1 A, Erythematous-violaceous maculopapular rash on the anterior trunk and neck. B, Erythematous-violaceous maculopapular rash on the posterior trunk with solitary bullous formations. C, Skin at 48 hours after onset of the rash, with formation of blisters.

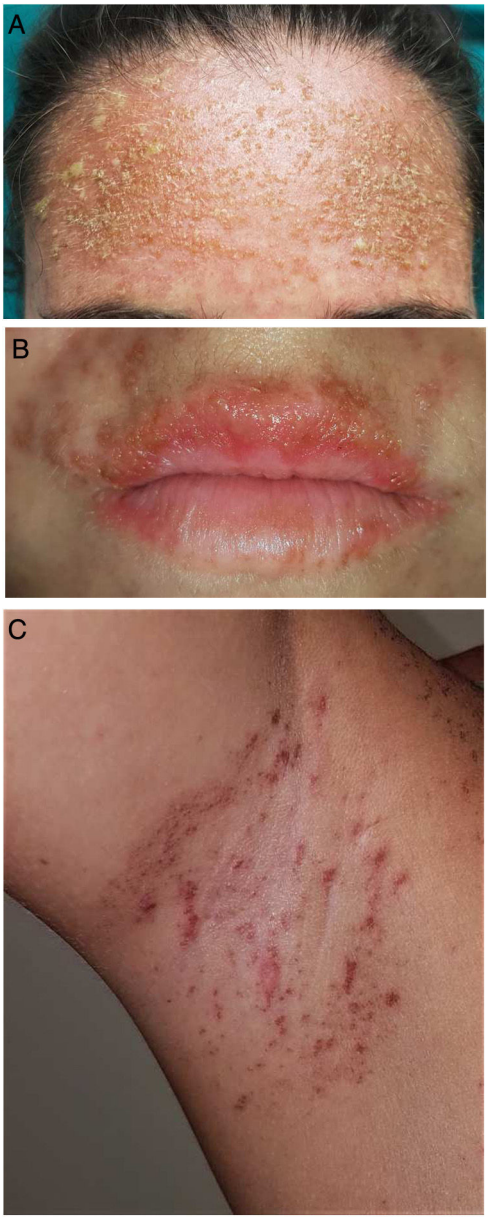

Figure 2 A, Erythematous, crusting rash with pustules on the forehead. B, Multiple vesicles on the area of the lips. C, Ecchymotic maculopapular rash on the axilla.

syndrome, although this is considered controversial. In fact, in the year 2000, Zeitouni et al.[6] defined new criteria for the diagnosis of Rowell syndrome. While the patient in the case we report fulfilled sufficient criteria to be diagnosed with this syndrome, our main suspicion was leflunomide-induced phototoxic reaction. Two months after the clinical picture had resolved, the patient underwent patch testing with the European photopatch series (Chemotechnique Diagnostics) and leflunomide 1%, 5%, and 10% in petrolatum, with UV-A radiation at 10 J/cm^2. The reading was negative at 3 minutes and at 48 and 96 hours.

Photosensitive rash is common in patients with SLE and is included in the diagnostic criteria. However, in the present case, we think that some of the drugs used in this disease could play a relevant role in triggering a phototoxic or photoallergic reaction. Differentiating clinically between phototoxic rash and photosensitive rash in SLE can prove difficult. Histopathology makes it possible to distinguish patients with true SLE, in which immunofluorescence reveals deposits of immunoglobulin M and C3 at the dermal-epidermal junction, findings that are absent in phototoxic rash. Photopatch testing should be considered as an additional test, with the objective of differentiating between phototoxic and photoallergic reactions. As for laboratory findings, a positive anti-Ro/SSA titer should be considered a risk factor for drug-induced SLE[7]. Furthermore, antihistone antibodies are detected in more than 95% of cases of drug-induced SLE, although they are also observed in 50%-70% of cases of SLE that are not drug-induced. In the case we report, the histone antibody test was negative, thus pointing us to a phototoxic reaction, as initially suspected.

In conclusion, we think that when assessing a patient with characteristics similar to those described here, the differential diagnosis should include drug-induced photosensitive rash, especially after initiation of treatment such as leflunomide, as in the present case. Additional tests, for example, patch (and photopatch) testing, are essential if we are to make an appropriate diagnosis.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Fischer TW, Bauer HI, Graefe T, Barta U, Elsner P. Erythema multiforme-like drug eruption with oral involvement after intake of leflunomide. Dermatology. 2003;207:386–9.
2. Schmutz JL, Barbaud A, Tréchot P. Leflunomide and Lyell syndrome. Ann Dermatol Venereol. 2009;136:395.
3. Pinto B, Dhir V, Krishnan S, Nada R. Leflunomide-induced DRESS syndrome with renal involvement and vasculitis. Clin Rheumatol. 2013;32:689–93.
4. Sues A, Sticherling M. Leflunomide in subacute cutaneous lupus erythematosus - two sides of a coin. Int J Dermatol. 2008;47:83–6.
5. Marzano AV, Ramoni S, Del Papa N, Barbareschi M, Alessi E. Leflunomide-induced ubacute cutaneous lupus erythematosus with erythema multiforme-like lesions. Lupus. 2008;17:329–31.
6. Zeitouni NC, Funaro D, Cloutier RA, Gagné E, Claveau L. Redefinf Rowell's syndrome. Br J Dermatol. 2000;142:343–6.
7. Srivastave M, Rencic A, Diglio G, Santana H, Bonitz P, Watson R, et al. Drug-induced, Ro/SSA-positive cutaneous lupus erythematosus. Arch Dermatol. 2003;139:45–9.

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Mitotic Rate as a Prognostic Factor in Melanoma: Implications for Disease Management☆

El índice mitótico como factor pronóstico y sus implicancias en el manejo del melanoma

To the Editor,

Sentinel lymph node (SLN) involvement is the most important prognostic factor in nonmetastatic melanoma. Predictors of nodal involvement include Breslow thickness, ulceration, and mitotic rate.[1]

The eight edition of the American Joint Committee on Cancer (AJCC-8) melanoma staging system removed mitotic rate as a predictive factor in melanoma because of its poor reproducibility secondary to low intraobserver and interobserver reliability.[2] The National Comprehensive Cancer Network Guidelines (version 1.2018), by contrast, suggest that SLN biopsy should be considered in patients with T1a melanoma (<0.8 mm, nonulcerated) and a mitotic rate of > 2 mitoses/mm^2, particularly if they are young. There is ample evidence that mitotic rate is predictive of SLN positivity (Table 1). According to a multicenter European study, SLN positivity was the most important prognostic factor in thin melanomas (n = 4249, Breslow thickness < 1 mm), and the only predictor of this positivity was a mitotic rate of > 2 mitoses/mm^2. T1a melanoma was associated with an overall risk of SLN positivity of 3.4% (or 1.2% for patients with a mitotic rate of 0 mitoses/mm^2), but this risk was 20% for > 2 mitoses/mm^2, which is even higher than that observed for T1b melanoma (8%).[3] In melanoma patients downstaged to T1a under the AJCC-8 criteria, the 3-year disease-free survival rate was 95%. This rate was significantly lower, however, at 80%, in those with a mitotic rate of > 3 mitoses/mm.[4] A US study of 17 204 patients with melanoma with a Breslow thickness of 0.01-1 mm reported a linear relationship between mitotic rate and SLN involvement. After adjustment for known prognostic factors, patients with a rate of > 1 mitoses/mm^2 were twice as likely to have SLN involvement than those with < 1 mitoses/mm^2. The risk of SLN involvement was 7.9% in patients with 1 mitosis/mm^2, but 21.8% and 44.5% for those with 5 and > 10 mitoses/mm^2, respectively. A recent European study that included a large cohort for the development (n = 3666) and validation (n = 4227) of a nomogram to improve the selection of patients with thin melanoma (Breslow thickness, < 1 mm) for SLN biopsy showed that age, Breslow thickness, a mitotic rate of > 1 mitosis/mm^2, ulceration, lymphovascular invasion, and regression > 75% were all significant predictors of SLN involvement. The resulting nomogram performed better than models based on current international recommendations at identifying which patients with thin melanomas should undergo SLN biopsy and showed that the higher

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