Low-Dose Oral Naltrexone for Darier Disease

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PRACTICE **POINTS**

- Consider low-dose naltrexone as a potential treatment option for patients with Darier disease, as it regulates opioid receptors and has shown benefits in enhancing epidermal differentiation, wound healing, and anti-inflammatory effects.
- Further research is needed to validate the efficacy and safety of low-dose naltrexone in treating Darier disease considering its observed clinical improvement in this single patient case.

To the Editor:

A 34-year-old Brazilian woman presented to the dermatology department with pruritic lesions on the neck and chest that had been present since adolescence. She reported a family history of Darier disease in her father. Physical examination revealed erythematous follicular papules on the neck, inframammary region, and abdomen (Figure 1A), as well as longitudinal bandlike leukonychia and distal nail splits on the fingernails (Figure 1B). Histopathology of a lesion on the back revealed compact hyperkeratosis and parakeratosis above an acantholytic cleft accompanied by dyskeratotic keratinocytes, including some corps ronds and grains, which supported the clinical impression of Darier disease (Figure 2). The typical clinical presentation along with the family history and histopathology confirmed the diagnosis. After therapeutic failure with topical corticosteroids and oral antibiotics for 3 months, low-dose oral naltrexone (4.5 mg/d) as monotherapy noticeably improved the lesions and pruritus within 2 months, with near-complete regression at 6 months, achieving disease stability (Figures 1C and 1D). The patient remained stable with no recurrence after 1 year of follow-up.

Darier disease is an autosomal-dominant genodermatosis caused by a mutation in the *ATP2A2* gene, which encodes the sarco/endoplasmic reticulum calcium ATPase, leading to defective intracellular calcium signaling and alterations in epidermal adhesion and keratinization.[1] Darier disease typically begins in adolescence and is aggravated by exposure to heat and friction. It is characterized by seborrheic distribution of painful and pruritic red-brown keratotic papules. Nail manifestations include longitudinal ridges—erythronychia and/or leukonychia—and grooves that end in a V-shaped notch. The differential diagnosis includes Hailey-Hailey disease, psoriasis, and pityriasis rubra pilaris.[1,2] The diagnosis is clinical and is confirmed by histopathology, which reveals suprabasal cleavage, acantholytic dyskeratosis, corps ronds, and grains. Treatment options are limited and include corticosteroids, oral and/or topical antibiotics, and systemic retinoids.[2]

Oral naltrexone has been used in Darier disease based on its observed effectiveness in Hailey-Hailey disease, considering the histopathologic similarities and alterations in calcium homeostasis in both conditions. Low-dose oral naltrexone (1-5 mg/d) increases the expression of opioid receptors (δ, μ, κ), enhancing its immunomodulatory and antinociceptive effects. The δ opioid receptor regulates the expression of desmoglein, improving epidermal differentiation and wound healing.[3] Activation of the δ and μ receptors increases intracellular calcium through the inositol phosphate pathway, which contributes to calcium homeostasis.[4] Naltrexone blocks the nonopioid toll-like receptor 4 found in keratinocytes and macrophages, exerting an anti-inflammatory effect by reducing proinflammatory cytokines.[3] Adverse events associated with low-dose naltrexone are

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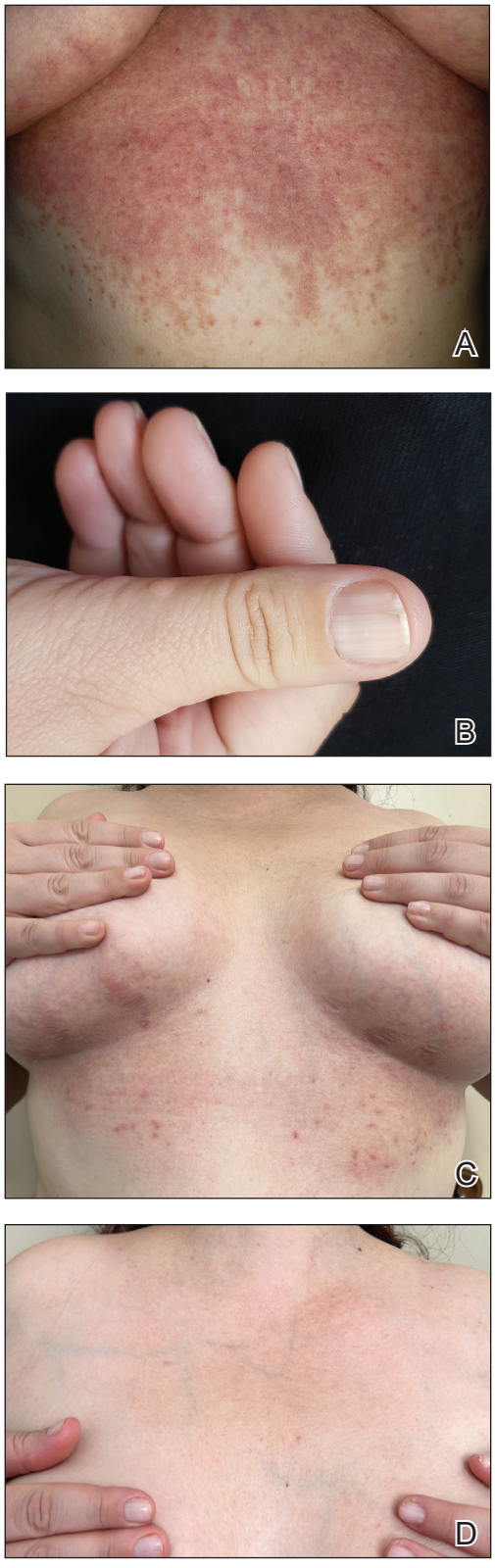

FIGURE 1. Darier disease. A, Erythematous follicular papules in the inframammary region at presentation. B, There also was a distal notch on the nail plate of the left thumb. C and D, After 6 months of low-dose oral naltrexone use, there were few isolated erythematous papules and decreased erythema in the inframammary and neck regions.

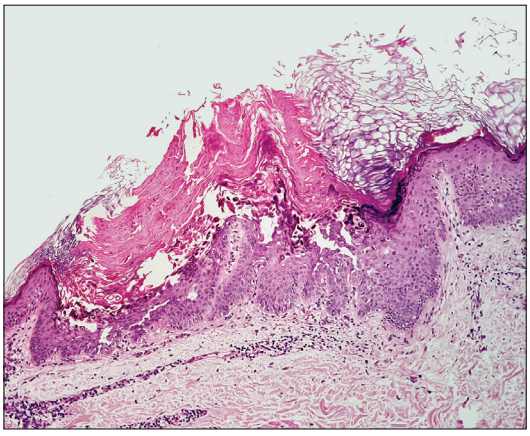

FIGURE 2. Histopathology demonstrated compact hyperkeratosis and parakeratosis above an acantholytic cleft accompanied by dyskeratotic keratinocytes, including some corps ronds and grains, which supported a diagnosis of Darier disease (H&E, original magnification ×10).

minimal, mostly mild, and often related to sleep disorders[3,5]; however, patients should undergo screening for prior opioid dependence, recent opioid usage, and signs of opioid withdrawal before initiating naltrexone treatment.[5]

Boehmer et al[6] used naltrexone (4.5 mg/d) and oral magnesium (200 mg/d) in 6 patients with inconsistent results, except for 1 case that concurrently used acitretin (25 mg/d) with satisfactory improvement. Pessoa et al[7] added naltrexone (4.5 mg/d) to oral isotretinoin (0.5 mg/kg/d) in 1 patient, resulting in notable improvement of lesions within 3 months.

In our patient with Darier disease, low-dose naltrexone demonstrated a substantial response as monotherapy after 2 months of treatment and nearly complete regression of lesions within 6 months, with no reported side effects after 1 year of follow-up. The use of low-dose naltrexone could be a promising and safe treatment option as monotherapy or in combination with conventional therapy for Darier disease; however, further studies are needed.

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