Low-dose naltrexone as treatment for epidermolysis bullosa pruriginosa–associated refractory pruritus

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INTRODUCTION

Dystrophic epidermolysis bullosa is a debilitating inherited mechanobullous disorder with a wide spectrum of clinical variability.[1] A rare subtype of epidermolysis bullosa, epidermolysis bullosa pruriginosa (EBP) results from an autosomal dominant or recessive *COL7A1* mutation.[2] EBP is characterized by severely pruritic lichenified and hypertrophic prurigo-like nodules and plaques secondary to chronic itching.[1-3] Prurigoform change occurs predominantly on lower legs, with head/neck, and truncal involvement occurring less frequently.[2] Milia and bullae are commonly observed.[1,2] Dystrophic nail changes may also be present as the first or only clinical sign of disease.[1,4]

Treatment of EBP is notoriously challenging. No standard first-line therapy currently exists, although topical corticosteroids, tacrolimus, cyclosporine, antihistamines, and thalidomide have been previously attempted.[5,6] In recent years there have been several reports of dupilumab and oral JAK inhibitors, such as tofacitinib, successfully managing EBP pruritus.[6,7] Here, we report a case of EBP pruritus which could not be managed with dupilumab, due to persistent pruritus and intolerable side effects, subsequently successfully treated with low-dose naltrexone.

Abbreviation used:

EBP: epidermolysis bullosa pruriginosa

CASE DESCRIPTION

A 35-year-old woman presented with a 15-year history of a severely pruritic lichenified papules and plaques with associated blisters and milia on her bilateral lower extremities and low back. She reported associated progressive burning, blistering, swelling, and reduced sensation of the bilateral lower extremities. Previous treatments included compression stockings, topical steroid creams, and a 3-month trial of phototherapy which was discontinued due to significant burning and discomfort. She reported a long-standing personal and family history of nail abnormalities, although no similar rash was noted among her family members.

Examination of the bilateral lower extremities demonstrated violaceous to hyperpigmented papules coalescing into confluent plaques with scattered milia and intact vesicles (Fig 1, *A* and *B*). To a lesser extent, on the medial sacrum, there were similar hyperpigmented thin plaques. Toe nail examination was notable for onychorrhexis with signs of nail matrix scarring resulting in micronychia (Fig 2). Fingernails did not show similar changes.

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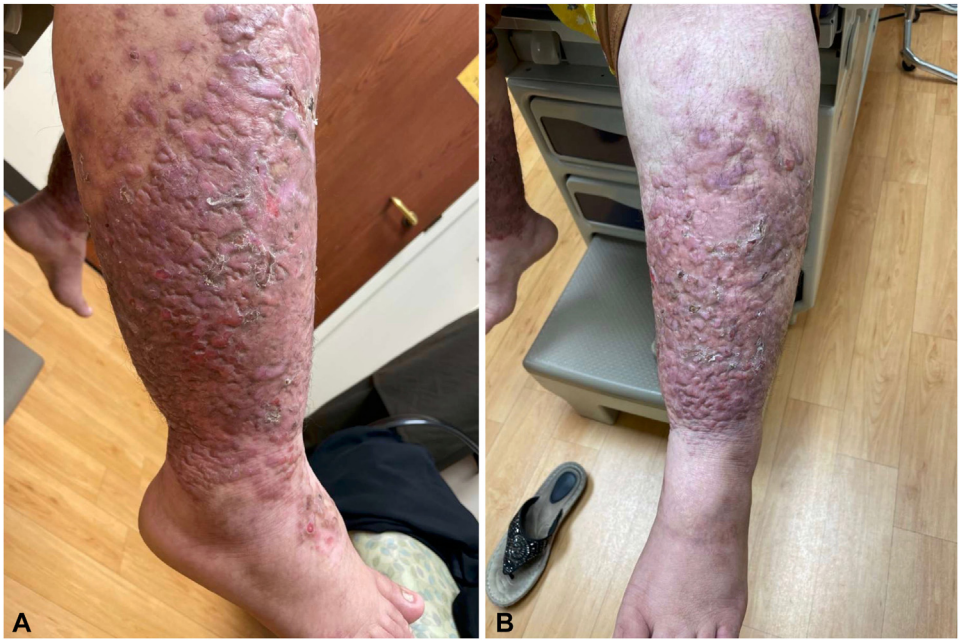

Fig 1. Clinical presentation of patient with epidermolysis bullosa pruriginosa upon initial dermatologic evaluation. **A,** *Right lower* extremity and (**B**) *left lower* extremity demonstrating violaceous to hyperpigmented confluent plaques with scattered milia and intact vesicles.

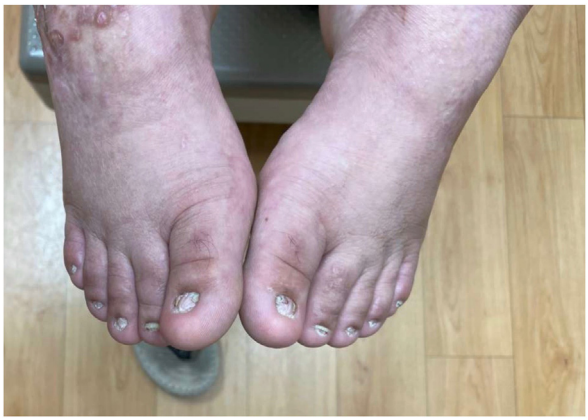

Fig 2. Dystrophic nail abnormalities in epidermolysis bullosa pruriginosa. Oychorrhexis with signs of nail matrix scarring resulting in micronychia.

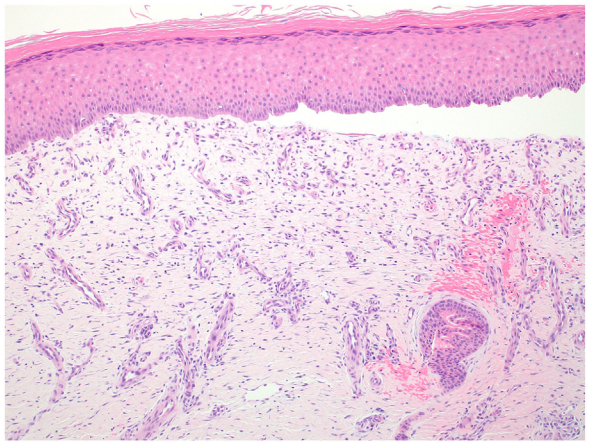

Fig 3. Histopathology. Punch biopsy specimens revealed a paucicellular subepidermal blister with associated dermal fibrosis and reactive vascular proliferation. Epidermal acanthosis is also seen as well as a sparse dermal interstitial inflammatory infiltrate composed primarily of lymphocytes and plasma cells (hematoxylin and eosin, original magnification ×100).

Punch biopsies of her right lower leg demonstrated a paucicellular subepidermal blister and extensive associated dermal fibrosis (Fig 3). Direct immunofluorescence was negative for immune deposits. Cumulatively, these findings were consistent with epidermolysis bullosa. The patient was subsequently referred for genetic testing, which was notable for a heterozygous *COL7A1* mutation associated with autosomal dominant dystrophic epidermolysis bullosa.

The patient was initiated on dupilumab and clobetasol 0.05% ointment with minimal improvement at her 2-month follow-up. After 11 weeks of treatment, dupilumab was discontinued due to persistent pruritus and debilitating conjunctivitis, as well as upper respiratory tract infections. A trial of low-dose (3 mg) naltrexone daily was initiated, using compounding to a 1 mg/mL solution.[8] Clobetasol ointment under occlusion was continued.

At her 3- and 5-month follow-up after naltrexone initiation, the patient reported a significant reduction in her lower extremity pruritus and burning.

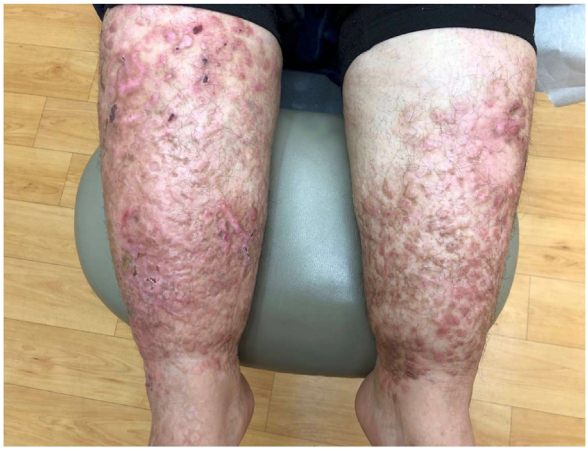

Fig 4. Response to low-dose naltrexone (3 mg by mouth daily) treatment. Follow-up evaluation after 5 months of low-dose naltrexone reveals a reduction in the number of scattered vesicles, decreased hyperpigmentation, and thinning of reticulated plaques, accompanied by a patient-reported significant improvement in pruritus.

Clinically, examination revealed thinning of the hyperpigmented lichenified plaques bilaterally with fewer scattered vesicles (Fig 4), a marked improvement from initial presentation. She noted that her pruritus would start to recur without her daily naltrexone dose.

DISCUSSION

Severe pruritus is the primary cause of morbidity and often the most distressing symptom of EBP. Histologic evaluation often reveals hyperkeratosis, acanthosis, a subepidermal blister or cleft, dermal fibrosis, and an associated vascular proliferation, which may be accompanied by a mild dermal chronic inflammatory infiltrate and milia cysts.[4] Direct immunofluorescence is typically negative.[1] Few treatments have proven effective at managing symptoms associated with EBP.

Dupilumab, a fully humanized monoclonal antibody, targets the interleukin 4 receptor alpha found on interleukin 4 and interleukin 13.[3] Interestingly, elevated IgE levels have been reported in patients with EBP without a history of atopy.[3] Recent reports have documented improvement of pruritus on dupilumab in patients with EBP who subsequently experienced a reduction in prurigo-like nodules and plaque formation.[3,7] Unfortunately, our patient continued to have pruritus while taking dupilumab and was unable to tolerate this secondary to recurrent ocular and upper respiratory tract infection side effects. Oral JAK inhibitors, through inhibition of skin sensory neurons by interleukin 31, tumor necrosis factor-α, and thymic stromal lymphopoietin, are promising as a therapeutic option for pruritus, including in cases of EBP.[6] Our patient was wary of the potential JAK inhibitor side effect profile; therefore, this treatment was not pursued.

Naltrexone, an opioid antagonist, is an alternative therapy that has gained increased use in dermatology. Opioid receptors, particularly the μ-opioid receptor, are found throughout the skin affecting various aspects of cell adhesion, migration, and proliferation.[9] Naltrexone exerts a dual effect through blockade of morphine-induced itch via the μ-opioid receptor, while also reducing inflammatory mediators including tumor necrosis factor-α, interleukin 6, and nitric oxide.[9] Prior studies have demonstrated that naltrexone yields symptomatic improvement of pruritus associated with atopic dermatitis, psoriasis, systemic sclerosis, lichen planopilaris, benign chronic pemphigus (Hailey-Hailey disease), and even nondermatologic conditions including cholestasis.[9]

Dosing of naltrexone bears implications for the treatment of pruritus due to modulation of endogenous opioid signaling.[10] One prior report documented naltrexone use in EBP, although a high dose (50 mg by mouth daily) was prescribed.[5] High-dose naltrexone results in continuous receptor binding, carrying the adverse risks of abdominal cramps, vomiting, and dizziness.[10] Low doses of naltrexone (1-5 mg) bind opioid receptors intermittently, increasing expression of both ligands and receptors to restore neuroepidermal homeostasis.[9,10] Therefore, intermittent binding of low-dose naltrexone may potentiate its efficacy in reducing pruritus, as seen in our patient.

While the exact mechanism of pruritus in EBP remains unknown and more detailed pharmacokinetic and pharmacodynamic evaluations are needed, our patient's response to treatment suggests that low-dose naltrexone may be used as a relatively inexpensive therapy that is very well-tolerated with a minimal risk profile. Further studies may evaluate the effect of low-dose naltrexone when used in conjunction with other therapeutics, such as JAK inhibitors,[6] for improved symptomatic and clinical management of EBP-associated pruritus.

Conflicts of interest

None disclosed.

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