Adalimumab therapy used successfully for recalcitrant Hailey-Hailey disease

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INTRODUCTION

Hailey-Hailey disease (HHD), or benign familial pemphigus, is an autosomal dominant blistering dermatosis characterized by recurrent painful vesicles and erosions involving intertriginous areas, with significant impact on quality of life.1 The classic histopathology findings include suprabasal and intraepidermal acantholysis. The disruption of epidermal junctions in HHD predisposes patients to secondary infections that further propagate the exacerbation and persistence of the disease.1

The management of HHD remains challenging given its recalcitrant nature as well as the lack of high-quality evidence and a consensus on its treatment. Traditional therapies, including topical and oral corticosteroids, antimicrobials, calcineurin inhibitors, and methotrexate, frequently fail to provide long-term remission.2 Other therapies with limited evidence include low-dose naltrexone, retinoids, lasers, dermabrasion, magnesium chloride, oral vitamin D, botulinum toxin A, 5-fluorouracil, apremilast, dupilumab, and etanercept.1-3 We describe a case of HHD refractory to multiple agents that was successfully treated with adalimumab, an anti–tumor necrosis factor (TNF)-α monoclonal antibody.

CASE REPORT

A 37-year-old woman presented with a 3-year history of biopsy-confirmed HHD and a positive family history. An examination revealed extensive hyperkeratotic, eroded, erythematous papules and plaques on the neck, chest, inframammary folds, and medial aspect of the thighs with evidence of excoriation. She had previously responded well to a combination of fluocinonide, fluconazole, tacrolimus, and doxycycline but experienced recurrence and progression of the disease following cessation of doxycycline because of a diagnosis of ulcerative colitis.

She showed initial improvement with minocycline, zinc oxide, fluocinonide, calcipotriene, and triamcinolone but experienced significant flare following methicillin-susceptible *Staphylococcus aureus* infection of the left side of the neck and left breast (Fig 1, A and B). Additional therapies trialed over the next several years included clobetasol, prednisone tapers, mupirocin, cephalexin, oral vitamin D, glycopyrrolate, magnesium chloride, and topical 5-fluorouracil. Despite the multiple therapies, she continued to experience recurrent, secondary infections and cycles of relapse and remission with a similar degree of cutaneous involvement (Fig 2, A and B).

Her HHD symptoms showed sustained improvement for the first time following initiation of adalimumab for ulcerative colitis at a maintenance dose of 40 mg every 14 days. She stopped all other interventions and had no further flares for 8 months. The cutaneous findings at her most recent clinic visit included waxy brown macules and papules with

Abbreviations used:

- HHD: Hailey-Hailey disease
- HSV: herpes simplex virus
- IL: interleukin
- TNF: tumor necrosis factor

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minimal residual erythema of the neck, axilla, and inframammary regions (Fig 3, A-C).

**DISCUSSION**

HHD is caused by a mutation in the *ATP2C1* gene, which encodes hSPA1C, a Ca²⁺/Mn²⁺ transporter located on the Golgi apparatus. Dysfunction of hSPA1C leads to calcium deposition in the Golgi lumen and abnormal processing and transportation of keratinocyte junctional proteins, resulting in epidermal acantholysis. Most of the traditional HHD therapies have focused on reducing overall inflammation. The utility of targeting specific pathways, including TNF-α, remains poorly understood, and the role of TNF inhibition in the treatment of HHD is not well characterized in the literature. Etanercept, a fusion protein TNF-α inhibitor, has been reported to induce long-term remission in a single case of HHD refractory to multiple therapies.

TNF-α is a proinflammatory cytokine implicated in the pathogenesis of many immune-mediated inflammatory diseases. Recent evidence has suggested that it is involved in the pathogenesis of HHD through its effects on calcium homeostasis. TNF-α has been shown to modify intracellular calcium signaling through multiple mechanisms, including stimulating calcium influx via binding of membrane calcium channels, inducing inositol phosphate turnover, and activating the expression of crucial proteins in calcium homeostasis. Naltrexone, another novel agent used in the treatment of HHD, is thought to modulate dysfunction of calcium transportation by inhibiting Toll-like receptor 4, leading to a subsequent reduction in the levels of nitric oxide, interleukin (IL) 6, and TNF-α. Collectively, these mechanisms introduce the biological plausibility of targeting TNF-α for the treatment of HHD.

Recent data have also suggested that TNF-α plays a role in increasing the risk of secondary infections in patients with HHD and Darier disease. Like HHD, Darier disease is an autosomal dominant disorder caused by a mutation in *ATP2A2*, leading to a calcium transport defect and abnormal keratinocyte junctional protein processing. Patients with either condition have disrupted epidermal barriers, leading to increased susceptibility to secondary infections, including herpes simplex virus (HSV). An in vitro study in 2021 showed that IL-6 and TNF-α enhanced
the growth of HSV-1 in well-differentiated keratinocytes. In turn, HSV-1–infected keratinocytes enhanced the production of IL-6 and TNF-α from mast cells via IL-33 expression, further propagating HSV growth. Clinically, this process correlates with the exacerbation of the symptoms of HHD and Darier disease following secondary infections. Although further investigation is needed, these findings offer a possible explanation for how TNF-α inhibition contributed to sustained remission of HHD symptoms in our patient, in whom multiple therapies had failed, by potentially decreasing the susceptibility to this infection.

Overall, the evidence for the use of TNF-α inhibitors in patients with HHD remains extremely limited in the literature. Our case adds to the paucity of literature by supporting the use of anti-TNF-α therapy for HHD, specifically with adalimumab.
Targeting the TNF-α pathway may confer additional benefits compared with other traditional therapies that also induce systemic immunosuppression. Further studies are needed to assess the role of TNF-α inhibition and adalimumab in the management of HHD.

Conflicts of interest
None disclosed.

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