SKIN

BRIEF ARTICLE

Utilizing Upadacitinib for the Management of Hailey-Hailey Disease

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ABSTRACT

Hailey-Hailey Disease is a rare disease associated with mutation of the ATP2C1 gene characterized by skin blistering and erosion. Here, we report a case of a patient with Hailey-Hailey disease who significantly improved after treatment with upadacitinib. A 55-year-old male with biopsy-confirmed Hailey-Hailey disease presented with a 20-year history of ill-defined, brightly erythematous, painful patches initially on the neck and subsequently involving the penile shaft. Following treatment with 30 mg of upadacitinib, the patient's neck ulcer gradually reepithelized. This case adds to the growing body of literature supporting the use of Janus kinase inhibitors as a therapeutic modality for this condition.

INTRODUCTION

Hailey-Hailey Disease (HHD) is a rare disease associated with mutation of the ATP2C1 gene characterized by skin blistering and erosion.[1] Dysregulation of the calcium ion concentration gradient within the endoplasmic reticulum and Golgi apparatus pump leads to impaired keratinocyte differentiation and cell-cell adhesion.[1] The prevalence of HHD is estimated to be approximately 1 in 50,000**,** and the condition is inherited in an autosomal dominant pattern.[2] Diagnosis of HHD can be established through clinical history, blood tests, and biopsies demonstrating abnormal keratinization and acantholysis. Janus kinase inhibitors (JAKi) have revolutionized the treatment of many dermatological conditions with a growing number of off-label indications.[3] In this article, we report a case of a patient with HHD who significantly improved after treatment with upadacitinib.

CASE REPORT

A 55-year-old male with biopsy-confirmed Hailey-Hailey disease presented with a 20-year history of ill-defined, brightly erythematous, painful patches initially on the neck (**Figure 1A**) and subsequently involving the penile shaft, scrotum, and thighs. Physical examination was also notable for a well-demarcated ulcer with granulation in the coronal sulcus and extending to the adjacent shaft (**Figure 2A**). He was previously treated with a variety of medications including ruxolitinib, botulinum toxin, intralesional steroids injections, tacrolimus, prednisone, and phototherapy without adequate treatment response. He initially reported improvement with topical ruxolitinib cream

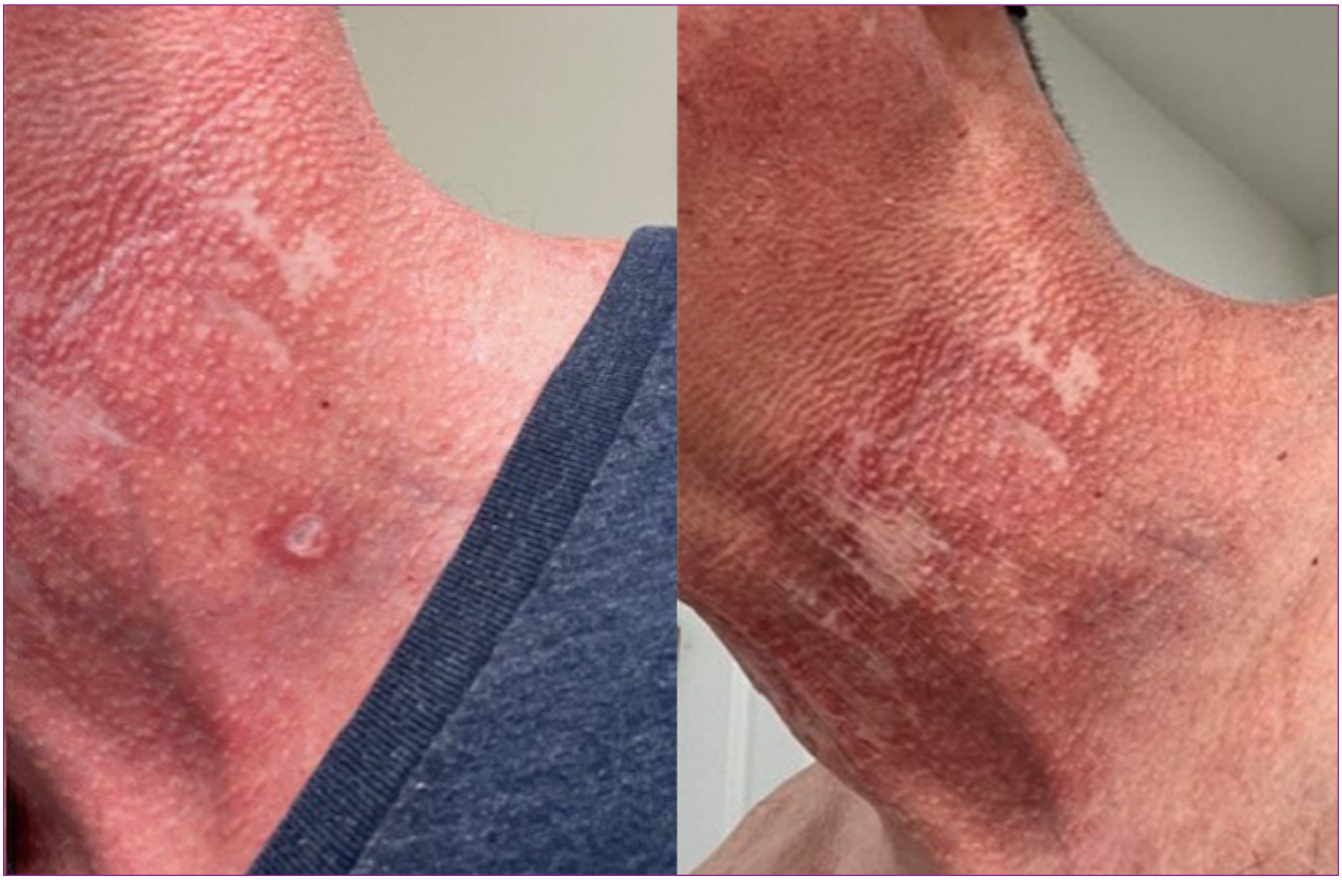

Figure 1. (A) Erythematous ulcer on the lower left neck with rough, hypopigmented patches on neck before initiating treatment with upadacitinib 30mg. (B) Resolved ulcer on the lower left neck after initiating treatment with upadacitinib 30mg.

but later experienced secondary treatment failure. At his initial visit, he was started on upadacitinib 15 mg, topical timolol, and domeboro solution. A consultation with plastic surgery led to light debridement of the penile ulcer and the application of becaplermin gel. At follow up, the inflamed and ulcerated patches on neck, left thigh, groin and scrotum greatly improved, and the neck ulcer gradually reepithelialized (**Figure 1B**). Given the positive treatment response, his upadacitinib dosage was increased from 15mg to 30 mg daily. Despite gradual flattening, the erythematous penile ulcer with granulation tissue remained persistent. Consultation with urology led to debridement of subcutaneous tissue and application of Kerecis, a fish skin product, in anticipation of a skin graft (**Figure 2B**).

DISCUSSION

JAKi are a class of therapeutics that block various JAK1, JAK2, JAK3, and TYK2 signaling pathways.[3] There is very limited literature evaluating the use of JAKi and small molecules for the treatment of HHD. A handful of case reports demonstrate successful treatment of HHD using tofacitinib, upadacitinib, and topical ruxolitinib.[4,5] Other treatment modalities such as apremilast, dupilumab, and tumor necrosis factor alpha blockers have also been utilized.[6] The JAK1/STAT signaling pathway via Th2 mediated interleukins (IL) 4 and 13 may be related to the molecular basis of HHD.[4] Upadacitinib and dupilumab both function by blocking IL-4 and IL-13 pathways,

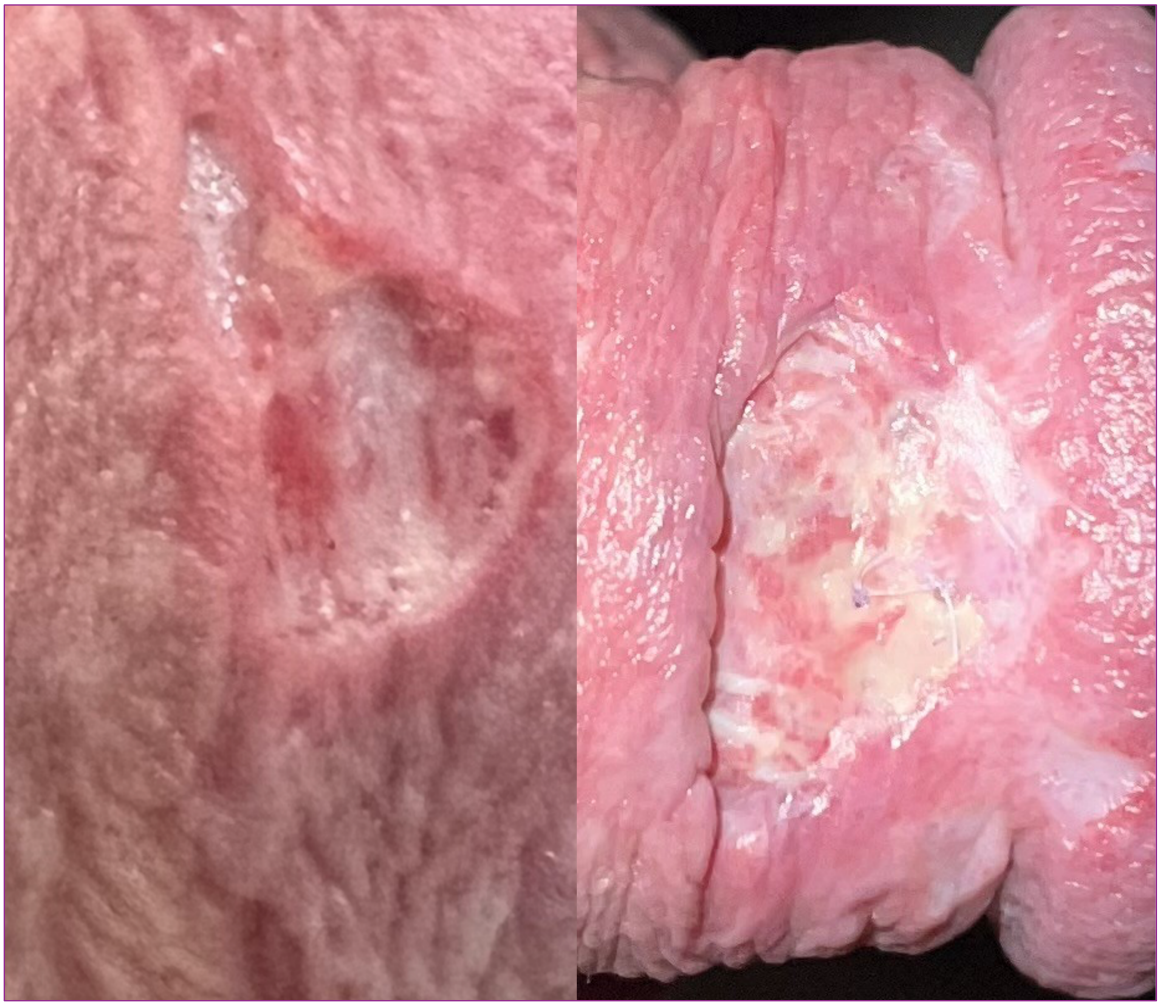

Figure 2. (A) Penile ulcer before initiating treatment with upadacitinib. (B) Penile ulcer following treatment with upadacitinib 30 mg and Kerecis grafting.

which has demonstrated good treatment response to HHD, suggesting that they may be implicated in calcium regulation within keratinocytes.[4] Our patient may have experienced a more durable treatment response to upadacitinib compared to ruxolitinib because of their respective selectivity profiles for the JAK pathway. Upadacitinib selectively inhibits JAK1, whereas ruxolitinib inhibits both JAK1 and JAK2.[3] Additionally, orally administrated medications have greater systemic effect as compared to topically administered medication. Our patient's neck ulcer demonstrated significant improvement and closure after initiating upadacitinib treatment. However, our patient's penile lesion likely did not respond as well due to decreased wound vascularization compared to his neck ulcer, therefore requiring surgical intervention. This unique case adds to the small, yet growing body of literature demonstrating the successful use of JAKi for HHD.

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