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Successful treatment of recalcitrant severe Hailey-Hailey disease with tofacitinib

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Abstract

Hailey-Hailey Disease (HHD) is a rare autosomal dominant skin disorder caused by mutations in the ATP2C1 gene, leading to impaired calcium ion regulation and cell adhesion, manifesting as recurrent blisters and macerated plaques in friction-prone areas. Standard treatments often provide inadequate control for some patients. Emerging therapies such as Janus Kinase (JAK) inhibitors have shown potential in treating inflammatory skin conditions. This case report details the treatment of a 62-year-old woman with a 22-year history of recalcitrant HHD, unresponsive to conventional therapies. The patient, with a significant family history of HHD experienced notable improvement after initiating tofacitinib. Marked clinical improvement was observed within one month, with sustained results over three months and no adverse events, highlighting the potential of JAK inhibitors as an effective treatment option for refractory HHD.

Keywords: Hailey-Hailey; JAK inhibitor; Tofacitinib.

Introduction

Hailey-Hailey Disease (HHD) is a rare autosomal dominant genodermatosis characterized by the presence of blisters and macerated plaques in areas of friction and sweating, particularly affecting the axillary and inguinal folds [1]. It is caused by mutations in the ATP2C1 gene, resulting in decreased calcium ion levels within cells and subsequent breakdown of cell adhesion [2]. The relapsing nature of HHD, coupled with superinfection, significantly diminishes the quality of life for affected individuals [3].

The primary treatment modalities for HHD typically include topical corticosteroids, calcineurin inhibitors, and antibiotics, with oral medications such as antibiotics, retinoids, and methotrexate also being utilized. However, a subset of patients remains resistant to standard treatment protocols [2]. Emerging therapies, such as Janus Kinase (JAK) inhibitors, have shown promise in various inflammatory and autoimmune skin diseases [4].

In this case report, we present a case of recalcitrant HHD successfully treated with a JAK inhibitor.

Case presentation

A 62-year-old woman with a 22-year history of pathology confirmed HHD went to dermatology clinic. The disease initiated in the sub mammary area and expanded in axillaries, inguinal folds and neck. She went through long term of oral prednisolone and antibiotics, and topical corticosteroids, but the disease wasn't controlled and had flares. She had a positive familial history of HHD in her father, sister and son, but all of them were controlled. She had hypothyroidism which is controlled with levothyroxine, HTN followed by hypophysis adenoma since 18 years ago. Other drugs include losartan and amlodipine. She lived in a warm area, unlike her sister and her disease is worsen by warmth and sweeting.

Due to the severity and unresponsively to conventional treatments, tofacitinib 5 mg twice a day was initiated for the pa-

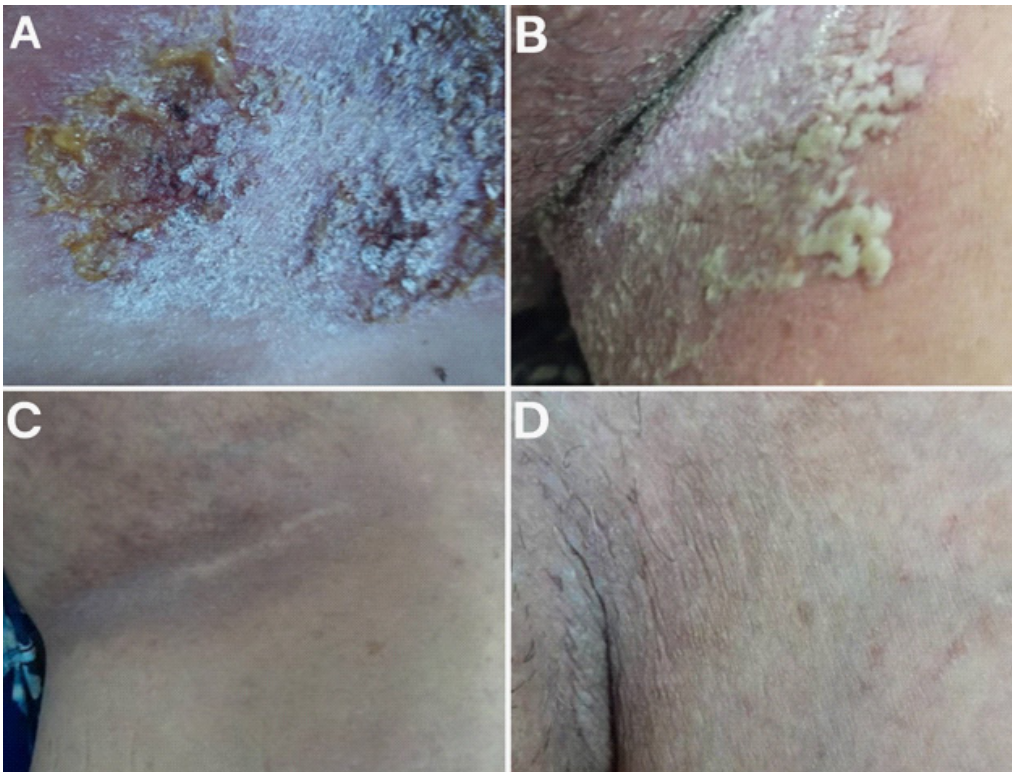

Figure 1: Sub mammary and inguinal fold before **(A,B)** and three months after initiating tofacitinib **(C,D).**

tient. After a month evident clinical improvement was obtained and satisfactory result without adverse events was maintained during 3 months of the follow-up (Figure 1).

Discussion

Tofacitinib is a JAK inhibitor that selectively inhibits JAK1 and JAK3 enzymes. This inhibition effectively limits the transmission of intracellular signals triggered by growth factors and cytokines such as interferon alfa/beta, interferon gamma, Interleukin (IL) 2, IL-4, IL-5, IL-6, IL-12, IL-13, IL-15, and IL-23 through the JAK-STAT pathway [4]. The JAK-STAT signaling pathway plays a major role in the pathogenesis of autoimmune diseases [5]. Tofacitinib, approved by the FDA for conditions such as rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis, has a wide range of applications in dermatology as well [6].

Despite the array of medications employed in treating Hailey-Hailey Disease (HHD), no specific treatment with satisfactory results has been proposed. Mutations in the ATP2C1 gene imply involvement of a $Ca2^{+}$-dependent signaling pathway in controlling cell-to-cell adhesion and epidermal differentiation in HHD. The fundamental mechanism underlying HHD pathogenesis involves diminished cellular adhesion due to ATP2C1 haploinsufficiency, leading to cellular stress, keratinocyte apoptosis, and the release of inflammatory cytokines.

The pro-inflammatory cytokines IL-6 and IL-8 might have a pivotal role in modulating ATP2C1 expression [2]. Therefore, it is hypothesized that JAK inhibitors could potentially benefit Hailey-Hailey Disease (HHD) treatment by regulating the immune response. In this study, oral tofacitinib yielded promising results in treating stubborn cases of HHD, marking the first investigation of tofacitinib's efficacy in HHD treatment to our knowledge.

Several studies have explored the use of JAK inhibitors for Hailey-Hailey Disease (HHD). In a case report by Khang et al. a combination of oral dupilumab and topical ruxolitinib 1.5% cream demonstrated satisfactory results in treating a stubborn case of HHD, with no flares or side effects observed during a five-month follow-up period [7]. Another case report by Yufen-li et al. suggested abrocitinib, a highly selective JAK1 inhibitor, as a potential alternative for recalcitrant HHD cases [8].

Additionally, a recent case report described the successful use of the Janus kinase (JAK)1/2 inhibitor baricitinib in a patient with Darier disease, which shares similar pathogenesis with HHD [9]. The patient showed improvement after one month of treatment with a dose of 4 mg per day, and the response was sustained for three months.

Furthermore, Murphy et al. demonstrated successful management of refractory Hailey-Hailey disease with upadacitinib, a novel JAK-1 inhibitor [10]. These studies collectively suggest that JAK inhibitors hold promise as potential therapeutic options for HHD cases resistant to conventional treatments.

These studies align with the findings of the current research. While the present study proposes tofacitinib as a satisfactory alternative for Hailey-Hailey Disease (HHD), it is recommended that further clinical trials with larger sample sizes and longer durations be conducted to fully assess the efficacy and safety of this novel application.

Conflicts of interest: The authors have no conflicts of interest to declare.

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