Navigating Diagnostic Complexity in Hailey-Hailey Disease: A Case Report with Clinical-histopathological Correlation

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Abstract: Hailey-Hailey disease (HHD), also known as benign familial pemphigus, is a rare autosomal dominant genodermatosis caused by mutations in the *ATP2C1* gene. These mutations impair keratinocyte adhesion and disrupt calcium homeostasis, leading to characteristic clinical and histopathological findings. Herein, we present the case of a 50-year-old male with a ten-year history of recurrent, pruritic, erythematous erosions and maceration in the left axilla and groin. Clinical examination revealed no systemic comorbidities or relevant family history. Histopathological analysis of skin biopsy demonstrated hallmark features, including epidermal hyperkeratosis, suprabasal and intraepidermal clefting, and acantholysis with the distinctive "dilapidated brick wall" appearance, confirming the diagnosis of HHD. Differential diagnoses, including intertrigo, Darier disease, and pemphigus vegetans, were excluded based on clinical and histological findings. The patient was managed with immunomodulators and topical antibiotics, with follow-up care focused on symptom alleviation and infection prevention. This case underscores the importance of correlating clinical and histopathological findings in diagnosing HHD and differentiating it from other intertriginous dermatoses. Despite its chronic and recurrent nature, timely and accurate diagnosis, coupled with individualized management, significantly enhances patient outcomes. This report also highlights the unique histological feature of acantholysis resembling a "dilapidated brick wall", pivotal in distinguishing HHD. Advances in understanding the molecular pathogenesis of ATP2C1 mutations hold promise for the development of targeted therapies, offering hope for more effective management of this challenging condition in the future.

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Introduction

Hailey-Hailey disease (HHD), commonly known as benign familial pemphigus, is an uncommon genetic dermatological condition characterized by an autosomal dominant inheritance pattern. It was first recognized by the Hailey brothers in 1939 (Michel, 1982). The condition results from a mutation in the *ATP2C1* gene. This gene aids in preserving cellular adhesion within the epidermis. A mutation in this gene disrupts desmosome activity, leading to disease manifestation (Prateek et al., 2016). Hailey-Hailey illness primarily affects the flexural regions, including the groin, neck, and axilla. It presents as blisters that rupture, leading to painful fissures, erosions, or plaques. Maceration and subsequent infections are common consequences (Sharma and Sharma, 2018). We documented a case of a 50-year-old male who exhibited itchy, erythematous erosions in the left axilla and left groin, subsequently identified as Hailey-Hailey disease through clinical and histological evaluation.

Case report

A 50-year-old man presented to the outpatient department of dermatology with a complaint of multiple erosions accompanied by itching, primarily in the flexural areas, for the past 12–13 years. On examination, erosions with crusting and maceration were observed over the lower abdomen and groin, while the bilateral axillae exhibited mainly post-inflammatory hyperpigmentation with very few erosions. (Figures 1 and 2 showing gross clinical appearance of Hailey-Hailey disease hyperpigmentation crust and erosion.) The patient reported that his symptoms worsened primarily during the summer. No involvement of other systems was noted, and there was no family history of a similar condition.

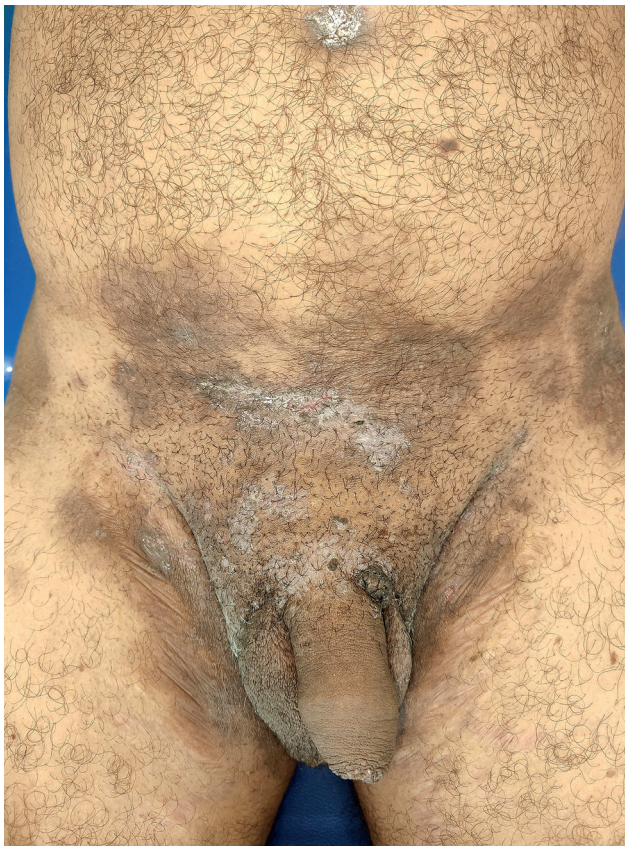

Figure 1: Clinical image of Hailey-Hailey disease showing hyperpigmentation and maceration and erosion over genital area.

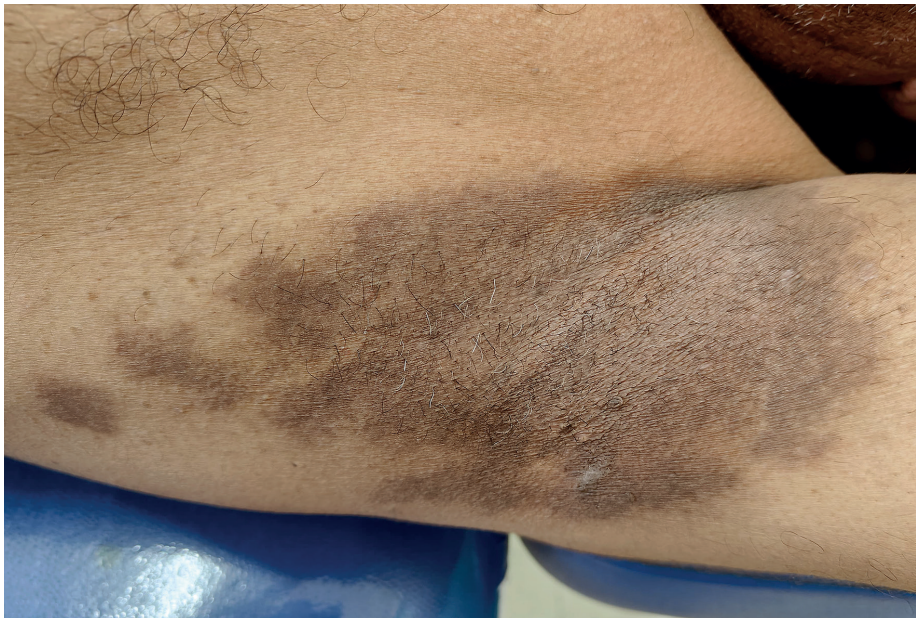

Figure 2: Clinical image of Hailey-Hailey disease showing hyperpigmentation and maceration and erosion over arm cubital fossa area.

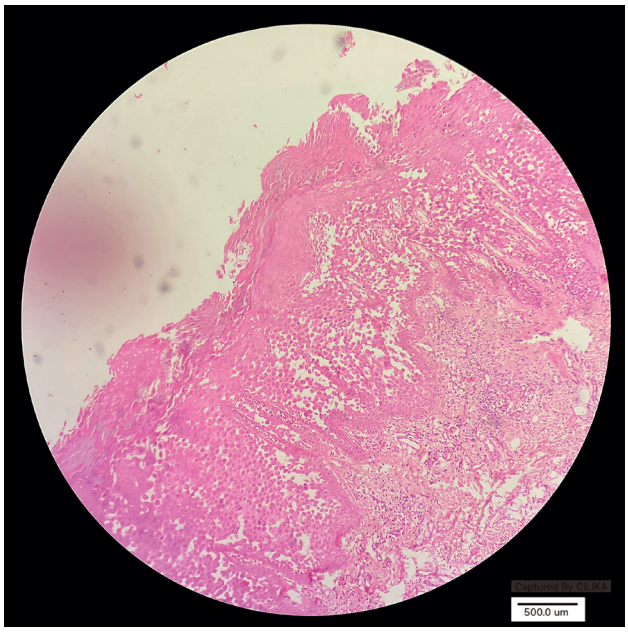

Figure 3: Photomicrograph of Hailey-Hailey disease showing hyperkeratosis, parakeratosis, regular acanthosis, dyskeratotic keratinocyte and acantholysis with dilapidated brick wall appearance (10× view, haematoxylin and eosin stain).

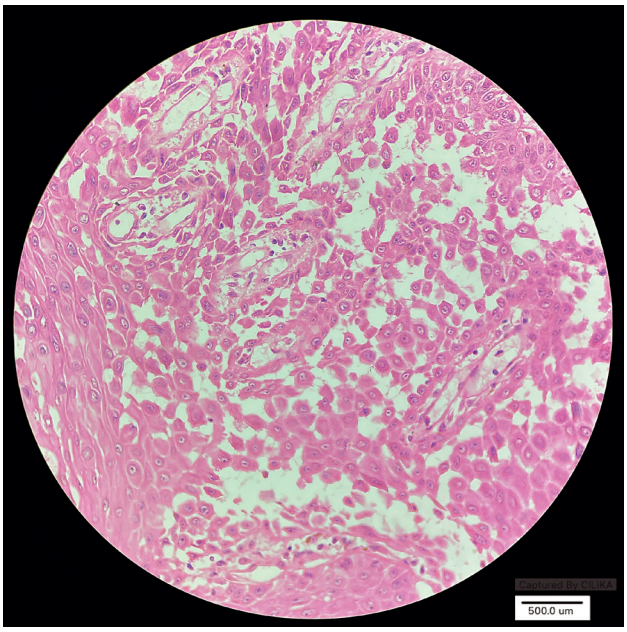

Figure 4: Photomicrograph of Hailey-Hailey disease showing hyperkeratosis, parakeratosis, regular acanthosis, dyskeratotic keratinocyte and acantholysis with dilapidated brick wall appearance (10× view, haematoxylin and eosin stain).

The patient's primary concern was pruritus. Routine blood investigations were within normal limits. There was no history of diabetes mellitus, fungal infections, or medication use. All standard hematological assessments were within normal parameters. There are no significant regards in the family history. A skin biopsy measuring 0.6×0.4 cm was obtained from the erosive areas of the left axilla and groin, and subsequently sent to the histopathology laboratory at the IPD complex for diagnostic evaluation. The term "IPD complex" refers to the in-patient department (IPD) complex, where admitted patients receive medical care and procedures such as skin biopsies are performed. Sections exhibit skin histology that includes epidermal hyperkeratosis, parakeratosis, and regular acanthosis. Supra-basal and intra-epidermal clefting is seen. A small number of dyskeratotic cells are also observed. Acantholytic keratinocytes exhibit a look suggestive of a dilapidated brick wall appearance. The superficial dermis has mild perivascular chronic inflammation. Skin appendages preserved. A diagnosis of Hailey-Hailey disease was established based on the clinical and histological findings. (Figures 3 and 4 showing photomicrograph microscopic appearance of Hailey-Hailey disease acantholytic keratinocytes with classical dilapidated brick wall appearance.)

He was counselled about the natural course of the disease and advised to wear loose clothing and avoid friction. Treatment with topical corticosteroids and oral antihistamines was initiated. The patient showed significant improvement within one month.

Discussion

Hailey-Hailey disease typically develops in early adulthood, often during the third or fourth decade of life, though it can occur at any age. The illness is quite rare, with a frequency of roughly 1 in 50,000, and around two-thirds of patients possess a familial history of the disorder (Burge, 1992; Ikeda et al., 1993; Calonje et al., 2020).

The transmembrane protein ATP2C1 is ubiquitous across all tissues, with high expression in keratinocytes. It functions as an ATPase responsible for transporting Ca^{2+} and Mn^{2+} into the Golgi apparatus, facilitating calcium influx into this organelle while lowering its cytoplasmic concentration. Mutations in the *ATP2C1* gene disrupt this ion gradient, causing cytosolic calcium accumulation, which leads to altered synthesis of junctional proteins, resulting in acantholysis, decreased mitochondrial ATP levels, leading to disruption of adherens junctions and increased reactive oxygen species, impairing keratinocyte proliferation and differentiation (Micaroni et al., 2016; Muncanovic et al., 2019).

Diagnosis is mainly based on clinical presentations, positive family history and characteristic histopathology which shows "dilapidated brick wall" appearance and negative immunofluorescent studies. Differential diagnosis includes intertrigo, eczema, Darier disease (DD) and pemphigus vegetans (Calonje et al., 2020).

Intertrigo and Hailey-Hailey disease can be distinguished by their clinical and histological

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characteristics. Intertrigo presents as erythematous, macerated, and moist lesions in skin folds, usually resulting from friction and moisture, whereas Hailey-Hailey disease is characterized by recurrent painful erosions, vesicles, and fissures that may become superinfected. Histopathologically, intertrigo exhibits nonspecific abnormalities such as spongiosis and mild inflammation, while Hailey-Hailey disease is marked by acantholytic changes that resemble a "dilapidated brick wall". Intertrigo is mostly caused by mechanical irritation and subsequent infection, while Hailey-Hailey disease is a genetic disorder associated with mutations in the *ATP2C1* gene, leading to impaired calcium homeostasis in keratinocytes (Romanelli et al., 2023).

Hailey-Hailey disease and Darier disease are clinically distinguished by the characteristics and distribution of their lesions, as well as their histological features. HHD is characterized by recurrent, vesicular, and erosive lesions predominantly in flexural regions, while DD is identified by keratotic papules and plaques in seborrheic areas. Histologically, HHD exhibits suprabasal acantholysis resembling a "dilapidated brick wall", whereas DD demonstrates acantholytic dyskeratosis characterized by huge ronds and grains (Kositkuljorn and Suchonwanit, 2019).

Pemphigus vegetans and Hailey-Hailey disease can be distinguished by their clinical and histological characteristics. Pemphigus vegetans generally manifests as vegetative plaques in intertriginous regions, frequently associated with oral mucosal involvement, while HHD is distinguished by vesicles and erosions absent of mucosal involvement. Pemphigus vegetans histologically demonstrates intraepidermal acantholysis with eosinophilic infiltration and pseudoepitheliomatous hyperplasia, unlike the "dilapidated brick wall" acantholysis observed in HHD (Jayapriya et al., 2021).

Management techniques encompass topical or systemic steroids, frequently combined with antibacterial medicines, to mitigate symptoms and avert infections. Notwithstanding advancements in treatment, the illness continues to pose management challenges because to its recurring and chronic characteristics (Ikeda et al., 1993).

Conclusion

This case highlights the clinical and histopathological features of Hailey-Hailey disease, emphasizing its distinct presentation and the critical role of histopathology in confirming the diagnosis. The characteristic "dilapidated brick wall" pattern of acantholysis remains a cornerstone for differentiation from other intertriginous dermatoses. Direct immunofluorescence (DIF) should be performed in the differential diagnosis of Hailey-Hailey and pemphigus vegetans (and other autoimmune bullous diseases), if available. DIF is negative in Hailey-Hailey disease.

Despite its chronic and recurrent nature, timely diagnosis and individualized management strategies, as demonstrated in this case, can alleviate symptoms and improve patient outcomes. Continued research into the molecular pathogenesis of ATP2C1 mutations offers hope for more targeted and effective therapies in the future.

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