Hailey-Hailey Disease: A Diagnostic Challenge

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PRACTICE **POINTS**

- Hailey-Hailey disease may present atypically with a late age of onset, involvement of nonintertriginous areas, and lack of clear exacerbating factors such as friction.
- A detailed history and physical examination as well as a high degree of suspicion can aid in diagnosing this uncommon disorder.

Hailey-Hailey disease (HHD) is an autosomal-dominant genodermatosis characterized by crusted macerated erosions, as well as velvety, dry, fissured plaques in the intertriginous areas. No predilection for sex or ethnic group has been reported. The typical age of onset is in the third decade of life. Diagnosis of HHD is suggested based on clinical morphology, location of lesions, family history, and histology demonstrating a characteristic dilapidated brick wall appearance of the epidermis. However, HHD often is misdiagnosed due to lack of knowledge of this uncommon disorder and its resemblance to other dermatoses. We describe an unusual presentation of HHD with a late age of onset and involvement of nonintertriginous regions.

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Hailey-Hailey disease (HHD), also known as benign familial chronic pemphigus, is an autosomal-dominant genodermatosis caused by mutations of the ATPase secretory pathway Ca^{2+} transporting 1 gene, *ATP2C1*.[1] It is characterized by crusted macerated erosions and velvety, fissured, hypertrophic plaques classically involving the intertriginous areas. The diagnosis is suggested by characteristic clinical morphology, involvement of the intertriginous areas, and a positive family history. Histology often confirms the diagnosis and demonstrates a characteristic dilapidated brick wall appearance. If there is a need to distinguish HHD from pemphigus, direct immunofluorescence studies also should be performed, which would be negative.[2,3] However, HHD often is misdiagnosed due to lack of knowledge of this uncommon disorder and its resemblance to other dermatoses of the intertriginous areas.[4] We present an unusual presentation of HHD with late onset and involvement of the skin of the abdomen and foot.

Case Report

A 61-year-old woman presented with a 3×4-cm fissured plaque with erosions and a peripheral yellow crust on the left side of the anterior abdomen (Figure 1A). There was another fissured plaque with surrounding erythema and scaling on the fifth digit of the right foot (Figure 1B). For the last 11 years, she periodically experienced erosive and scabbing skin plaques under the breasts and on the axillae and groin. Her mother and maternal grandfather had a history of similar skin lesions. Due to a suspicion of HHD, a skin biopsy specimen of the abdominal plaque was performed, which demonstrated epidermal acanthosis and suprabasal acantholysis with lacunae formation (Figure 2). There was uneven thickening of the epidermal keratin layer with parakeratotic nests. The upper layer of the

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The authors report no conflict of interest.

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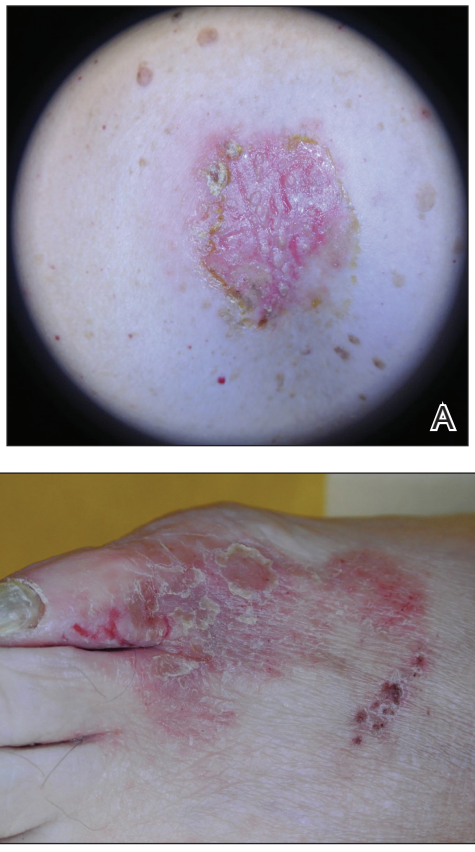

FIGURE 1. A, Hailey-Hailey disease of the left side of the anterior abdomen with a characteristic erythematous, hypertrophic, fissured plaque with erosions. B, A fissured plaque with surrounding erythema and scaling on the fifth digit of the right foot.

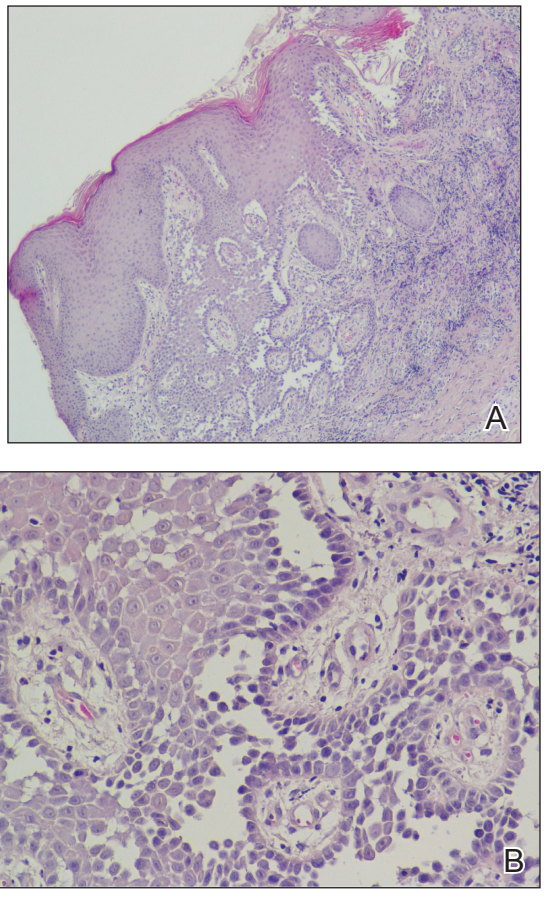

FIGURE 2. A, Histopathology revealed separation of keratinocytes, forming a dilapidated brick wall appearance (H&E, original magnification ×4). B, Acantholysis demonstrated separation of keratinocytes (H&E, original magnification ×20).

dermis demonstrated edema and focal fibrosis, enlarged capillaries, and pericapillary lymphohistiocytic infiltration with eosinophils and neutrophils. Accordingly, a diagnosis of HHD was established.

Comment

Hailey-Hailey disease occurs in 1 to 4 per 100,000 individuals without predilection for sex or ethnic group.[5-9] Onset usually occurs after puberty, most commonly in the third decade of life.[8,10-12] Mutations of the *ATP2C1* gene on band 3q22.1 cause haploinsufficiency of Ca^{2+}/Mn^{2+}−ATPase protein 1 (hSPCA1) that alters the intracellular calcium gradient, leading to disruptions in assembly and trafficking of desmosomal proteins to the cell membrane. Consequently, altered intercellular connections and acantholysis of the epidermis occur.[1,13-16]

Hailey-Hailey disease initially manifests as grouped flaccid vesicles that rupture easily, leaving behind crusted erosions and dry, scaly, eczematous patches.[17,18] Over time, velvety, fissured, and hypertrophic plaques develop. Up to 80% of patients experience secondary bacterial and fungal superinfections that may cause vegetative or malodorous plaques.[9] Although HHD has no specific treatment, symptoms are managed with topical corticosteroids and antimicrobial agents. Patients should be advised to avoid irritants such as friction, sunlight, or sweat. For severe cases, botulinum toxin type A, laser therapy, dermabrasion, and surgery have been utilized with variable success.[19-22] The responsiveness of HHD to corticosteroids and antimicrobial agents facilitates misdiagnosis as intertrigo, erythrasma, or dermatophytosis.

Our patient presented with late-onset HHD (age, 50 years) compared to the typical age of onset in the third decade of life.[8] Furthermore, her presentation was atypical for HHD, which characteristically affects intertriginous areas due to sweat, heat, friction, and microorganisms. Hailey-Hailey disease involving the abdominal skin is unusual, as it typically occurs in regions of friction such as the belt area.[23] Our patient lacked a history of friction or trauma at the site of the abdominal plaque. In addition, HHD involving the feet is exceedingly rare. It is plausible that friction and heat caused by footwear may have predisposed her to these skin changes.

Conclusion

This case highlights the difficulties of diagnosing HHD, especially if it appears in atypical locations.[24] Obtaining a thorough family history and detailed dermatologic examination as well as maintaining a high level of suspicion can assist in diagnosing this uncommon disorder.

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