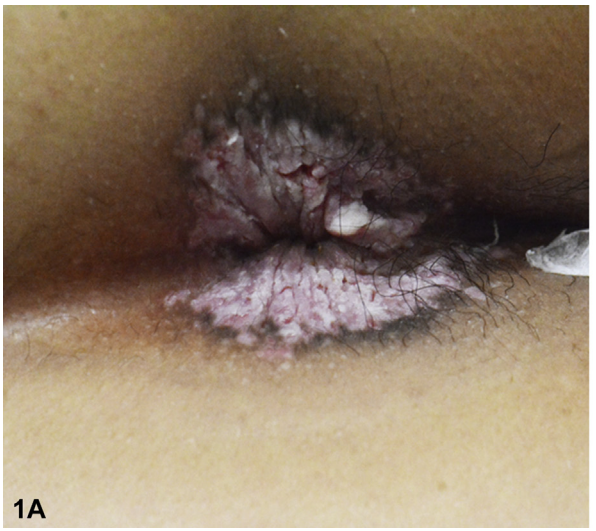
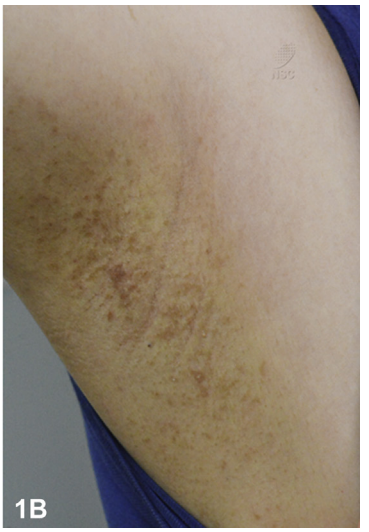
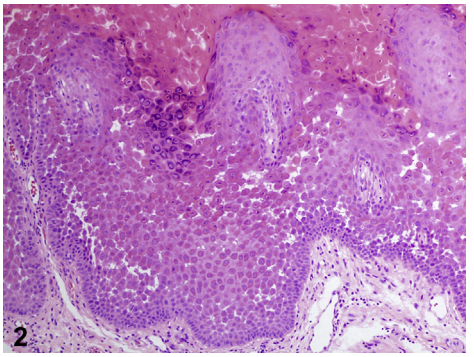
Persistent perianal "warts"

Rayson Rui Sheng Lee, MD,[a] Sophie Carrie Shan Cai, MD,[b] Hui-Yi Chia, MBBS,[b] and Hazel H. Oon, MD[b]
Singapore, Singapore

Key words: Darier disease; Hailey-Hailey disease; pemphigus; perianal warts.







CASE

A 31-year–old woman presented with a 5-year history of painful and pruritic perianal lesions previously treated with topical imiquimod, topical podophyllin, and cryotherapy, unsuccessfully. Her husband was her only sexual partner over the previous 5 years. She denied a history of anal intercourse. Screening for sexually transmitted infections was unremarkable. Perianal examination showed verrucous fissured plaques (Fig 1, *A*) with no malodor. Keratotic brown papules with few scattered erosions later developed on both axillae (Fig 1, *B*) and groin folds. Her sister, father, and grandfather had similar rashes on their neck and axillae. Her nails were normal. A punch biopsy was performed (Fig 2).

From the Tan Tock Seng Hospital, Singapore[a] and the National Skin Centre, Singapore.[b]
Funding sources: None.
IRB approval status: Not applicable.
Correspondence to: Rayson Rui Sheng Lee, MD, Tan Tock Seng Hospital, 11 Jln Tan Tock Seng, Singapore 308433, Singapore. E-mail: rayson.lee@mohh.com.sg.

JAAD Case Reports 2022;21:116-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.09.046

Question 1: What is the most likely clinical diagnosis?

A. Condyloma acuminata

B. Darier disease (DD)

C. Hypertrophic herpes simplex virus infection

D. Hailey-Hailey disease (HHD)

E. Giant condyloma of Buschke-Löwenstein

Answers:

A. Condyloma acuminata — Incorrect. Condyloma acuminata is caused by the human papillomavirus and appears as papular, verrucous lesions. This is less likely in the absence of a positive contact/sexual history. The presence of erosions in her axillae and positive family history suggests HHD.

B. DD — Incorrect. DD presents as hyperkeratotic papules to plaques that favor a seborrheic distribution. Nail involvement is common. While limited perianal disease may appear similar to condylomata and HHD, the positive family history of erosions in intertriginous areas is more suggestive of HHD.

C. Hypertrophic herpes simplex virus infection — Incorrect. Hypertrophic herpes simplex virus presents as ulcerated nodules in the anogenital region and are episodic. HIV coinfection is a strong predisposing factor and is absent here.

D. HHD — Correct. HHD presents as inconspicuous, fragile vesicles that progress to macerated erosions and crusting, mainly in intertriginous areas. Limited disease in the perianal region frequently presents in the papular form, as in this patient.[1] Her father also had HHD.

E. Giant condyloma of Buschke-Löwenstein — Incorrect. This condition is a low-grade, well-differentiated, verrucous variant of squamous cell carcinoma and may present in the anogenital region as a slow-growing, warty tumor. These squamous cell carcinoma variants tend to appear larger and more protuberant.

Question 2: What is the genetic defect associated with this condition?

A. Calcium adenosine triphosphatase (ATPase) of the Golgi apparatus (*ATP2C1*)

B. Calcium ATPase of the endoplasmic reticulum (*ATP2A2*)

C. Collagen type V alpha 1 chain (*COL5A1*)

D. Type I keratin, basal type (*KRT14*)

E. Adenosine triphosphate (ATP) -binding cassette, subfamily C, member 6 (*ABCC6*)

Answers:

A. Calcium ATPase of the Golgi apparatus (*ATP2C1*) — Correct. HHD is an autosomal dominant disorder caused by a mutation in *ATP2C1*, which facilitates intracellular calcium homeostasis. Dysfunction results in acantholysis, causing vesicles to appear in intertriginous areas.[2]

B. Calcium ATPase of the endoplasmic reticulum (*ATP2A2*) — Incorrect. DD is an autosomal dominant disorder caused by a mutation in *ATP2A2*, which also facilitates intracellular calcium homeostasis. Dysfunction causes acantholysis and dyskeratosis, which manifests as crusted papules to plaques in a seborrheic distribution.[2]

C. Collagen type V alpha 1 chain (*COL5A1*) — Incorrect. Ninety percent of classical Ehlers-Danlos syndrome is caused by a mutation in *COL5A1* and *COL5A2*, which are integral for fibrillogenesis. Impairment causes fragile, velvety skin, among other skeletal and ligamental issues.

D. Type I keratin, basal type (*KRT14*) — Incorrect. Epidermolysis bullosa simplex is caused by mutations in *KRT14* expressed in basal keratinocytes.[3] Disruption causes friction-induced blistering.

E. ATP-binding cassette, subfamily C, member 6 (*ABCC6*) — Incorrect. Pseudoxanthoma elasticum is caused by a mutation in *ABCC6*, which is an ATP efflux transporter protein on hepatocytes.[3] Reduced circulating ATP degradation products causes mineralization within tissues, including the skin, presenting as yellow or hyperpigmented papules on the neck and intertriginous areas.

Question 3: Which of the following histopathologic features is characteristic of this condition?

A. Suprabasal acantholysis with a "dilapidated brick wall" appearance

B. Koilocytosis in the epidermis

C. Subcorneal pustule

D. Subepidermal blister

E. Suprabasal epidermal acantholysis with a "tombstone pattern"

Answers:

A. Suprabasal acantholysis with a "dilapidated brick wall" appearance — Correct. Histology in HHD shows acantholysis among suprabasal keratinocytes, resulting in suprabasal clefts and a "dilapidated brick wall" appearance from the layers of detached keratinocytes. HHD has diffuse mild dyskeratosis, compared to DD, where dyskeratosis manifests focally as "corps ronds" or "grains."[4] Direct immunofluorescence is negative—distinguishing HHD from pemphigus.

B. Koilocytosis in the epidermis — Incorrect. Koilocytosis is seen in the epidermis of cells infected by a variety of viruses, most classically human papillomavirus.

C. Subcorneal pustule — Incorrect. Sneddon-Wilkinson disease presents as relapsing sterile pustular dermatoses. Histology shows subcorneal neutrophilic accumulation without spongiosis or acantholysis.[5]

D. Subepidermal blister — Incorrect. These are present in patients with pemphigoid disorders as well as others, including dermatitis herpetiformis and epidermolysis bullosa acquisita. HHD, on the other hand, presents with suprabasal acantholysis.

E. Suprabasal epidermal acantholysis with a "tombstone pattern" — Incorrect. This is the classic histologic description for patients with pemphigus vulgaris.[4]

Abbreviations used:

ATP: adenosine triphosphate
ATPase: adenosine triphosphatase
DD: Darier disease
HHD: Hailey-Hailey disease

Conflicts of interest

None disclosed.

REFERENCES

1. Langenberg A, Berger TG, Cardelli M, Rodman OG, Estes S, Barron DR. Genital benign chronic pemphigus (Hailey-Hailey disease) presenting as condylomas. *J Am Acad Dermatol*. 1992;26:951-955.
2. Dhitavat J, Fairclough RJ, Hovnanian A, Burge SM. Calcium pumps and keratinocytes: lessons from Darier's disease and Hailey-Hailey disease. *Br J Dermatol*. 2004;150:821-828.
3. DeStefano GM, Christiano AM. The genetics of human skin disease. *Cold Spring Harb Perspect Med*. 2014;4(10):a015172.
4. See SHC, Peternel S, Adams D, North JP. Distinguishing histopathologic features of acantholytic dermatoses and the pattern of acantholytic hypergranulosis. *J Cutan Pathol*. 2019;46:6-15.
5. Sneddon IB, Wilkinson DS. Subcorneal pustular dermatosis. *Br J Dermatol*. 1956;68(12):385-394.