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Dermoscopic and reflectance confocal microscopic presentation of Hailey-Hailey disease: A case series

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Abstract

Background/purpose: Hailey-Hailey disease is a rare inherited acantholytic skin disorder characterized by heterogeneous clinical presentation. Its differential diagnosis might be wide, including other genodermatoses, inflammatory, and infectious skin diseases. Although histopathology remains as diagnostic gold standard, noninvasive techniques such as dermoscopy and reflectance confocal microscopy may assist clinical examination. Herein, we aim to further characterize the dermoscopic and reflectance confocal microscopic presentation of Hailey-Hailey disease with histologic correlation.

Methods: Eight patients with Hailey-Hailey disease were consecutively recruited. All patients were examined using dermoscopy and reflectance confocal microscopy.

Results: In all cases, dermoscopy enabled the visualization of polymorphous vessels, including glomerular and linear-looped vessels, within a pink-whitish background. Reflectance confocal microscopy revealed wide suprabasilar partial acantholysis and clefting, crusts, dilated papillae with tortuous vessels, and inflammatory cells. Dyskeratosis, uplocated papillae, and adnexal sparing were also observed.

Conclusion: Although definite diagnosis was obtained by histopathology in all cases, dermoscopy and reflectance confocal microscopy allowed the identification of common features (even in cases with dissimilar clinical presentation) that may support an early diagnosis of Hailey-Hailey disease, and its differentiation from other more frequent skin disorders.

KEYWORDS

acantholysis, dermoscopy, familial benign chronic pemphigus, genodermatosis, Hailey-Hailey disease, reflectance confocal microscopy

1 | INTRODUCTION

Hailey-Hailey disease (HHD) or familial benign chronic pemphigus is a rare autosomal dominantly inherited acantholytic skin disorder. However, positive family history is only obtained in about two-thirds of patients, with variable phenotypic expression within affected family members.[1,2] HHD is known to be caused by mutations in ATP2C1 on chromosome 3q21-24. This gene encodes a Ca^{2+}/Mn^{2+} ATPase which is a calcium pump present on the Golgi apparatus.[3,4] Mutations will result in calcium deposition failure, ending in desmosomal separation, keratinocyte adhesion defects, and acantholysis.[5] Skin lesions usually develop in the second to fourth decades of life, with equal sex incidence. There is a predilection for flexural regions at sites of minor trauma, friction, and heat exposition, such as axillae, groins, lateral aspects of the neck, and inframammary folds in women. Primary lesions consist of transitory and flaccid vesicles and bullae on erythematous skin, soon replaced by erosions, fissures, crusts, and circinate, scaly, macerated plaques or chronic vegetations. Longitudinal white nail bands can also be a valuable diagnostic clue. Postinflammatory hyperpigmentation is common.[6]

TABLE 1 Characteristics of the eight studied patients with the diagnosis of Hailey-Hailey disease

Patient number	1	2	3	4
Clinical features				
Age, y/sex	35, F	55, F	27, M	55, M
Time since onset, y	8	15	2	20
Location	Neck, axillae, inframammary folds, groins, white longitudinal nail bands	Groins	Trunk (dorsal region)	Axillae, groins
Appearance	Circinate and vegetating plaques, flaccid vesicles, erosions, fissures, yellowish scales, and crusts	Vegetating plaques	Circinate plaques, erosions, fissures, yellowish scales, and crusts	Circinate and vegetating plaques, flaccid vesicles, erosions, fissures, yellowish scales, and crusts
Positive family history	+	+	+	+
Dermoscopy				
Polymorphous vessels	+	+	+	+
Glomerular vessels	+	+	+	+
Linear-looped ("spiral") vessels	+	+	+	+
Coiled vessels	–	–	–	–
Peripheral distributed vessels	–	–	–	+
Pink-whitish background	+	+	+	+
Pink-yellowish background	–	–	–	–
Scales and crusts	+	–	+	+
Erosions	+	+	+	+
Reflectance confocal microscopy				
Epidermis				
Crusts	+	+	+	+
Hyperkeratosis	+	+	+	+
Acanthosis	+	+	+	+
Disarranged epidermal pattern	+	+	+	+
Partial acantholysis (dilapidated brick wall)	+	+	+	+
Intraepidermal clefts/ vesicles	+	+	+	+
Dyskeratosis	+	–	–	–
Bright inflammatory cells	+	–	–	–
Adnexal sparing	+	+	+	+
Uplocated papillae	+	–	–	–
Dermal-epidermal junction				
Dilated papillae	+	+	+	+
Dilated, tortuous vessels	+	+	+	+
Bright inflammatory cells	+	–	–	–
Superficial dermis				
Bright inflammatory cells	+	–	–	–

Y, years; F, female; M, male.

Clinical differential diagnoses include candidiasis, inverse psoriasis, tinea corporis, allergic or irritant contact dermatitis, and Darier disease. Vegetating flexural lesions may be similar to those of pemphigus vegetans.[7-9]

Histological examination of established HHD lesions reveals widespread acantholysis with suprabasilar vesicle or bulla formation. Acantholysis is typically incomplete with keratinocytes

5	6	7	8	Total
48, F	54, M	27, M	49, F	
12	18	1	8	
Axillae, inframammary folds, groins	Axillae, groins, limbs	Axillae	Axillae, trunk (lumbar region)	
Circinate plaques, brown/yellowish scales, and crusts	Circinate plaques	Circinate plaques, flaccid vesicles, erosions, yellowish crusts	Circinate plaques, flaccid vesicles, erosions, yellowish crusts	
+	–	–	–	5/8
+	+	+	+	8/8
+	+	+	+	8/8
+	+	+	+	8/8
–	+	–	–	1/8
–	+	+	+	4/8
–	–	+	+	6/8
+	+	–	–	2/8
+	–	+	+	6/8
+	–	+	+	7/8
+	+	+	+	8/8
+	+	+	+	8/8
+	+	+	+	8/8
+	+	+	+	8/8
+	+	+	+	8/8
+	+	+	+	8/8
–	+	–	+	3/8
+	+	+	+	5/8
+	+	+	+	8/8
–	+	–	+	3/8
+	+	+	+	8/8
+	+	+	+	8/8
+	+	+	+	5/8
+	+	+	+	5/8

retaining some connections giving a "dilapidated brick wall" appearance. Adnexal structures are usually spared, and dyskeratotic cells are only occasionally observed. Hyperkeratosis, parakeratosis, acanthosis, and villi projections (from dermal papillae lined by a single layer of basal cells) protruding into blister cavities can also be seen. Direct immunofluorescence (DIF) is negative.[10-12]

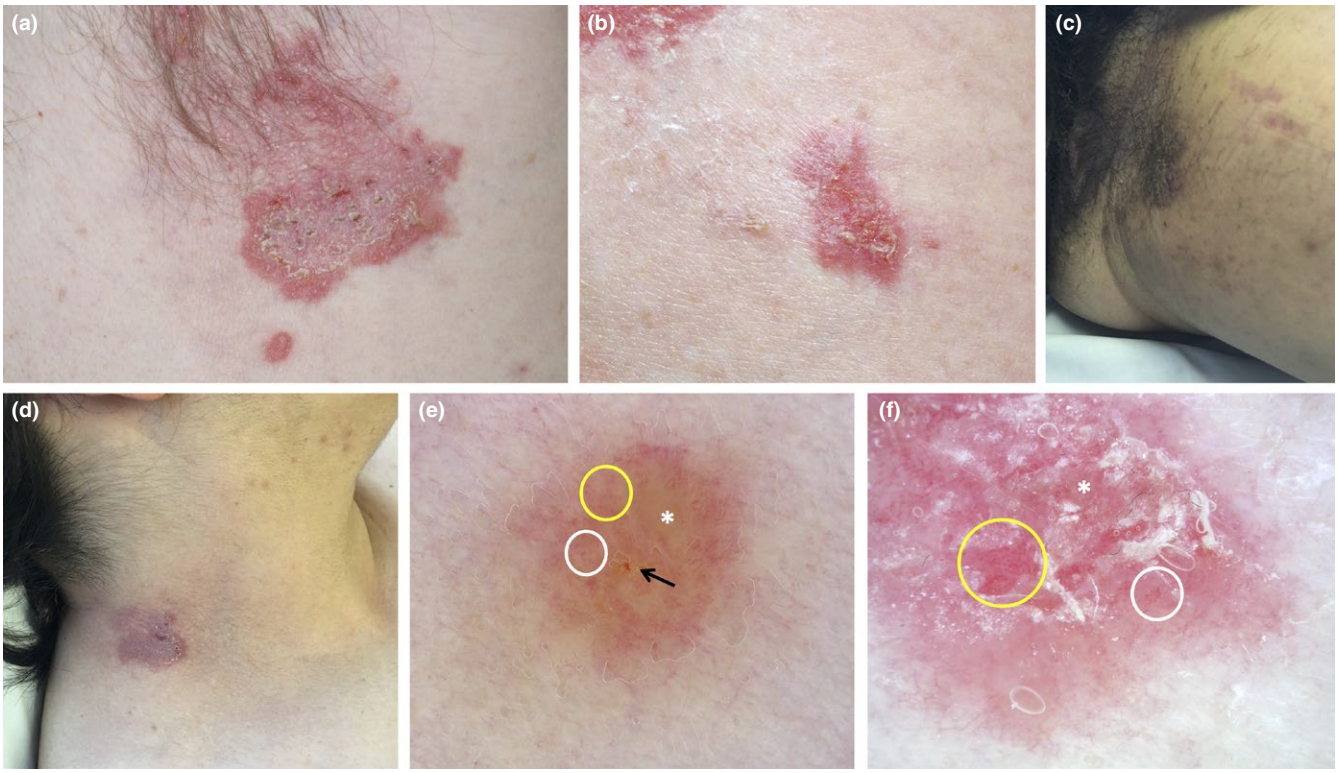

FIGURE 1 Haley-Hailey disease: clinical and dermoscopic appearance. A, Patient 7: Erythematous, circinate plaque of the left axilla; erosions and yellowish crusts are also observed. B, Patient 8: Flaccid vesicles on erythematous skin located on the lumbar region. C, Patient 1: vegetating plaques on the left groin. D, Patient 1: circinate, eroded plaque on the right lateral aspect of the neck. E, Patient 7: dermoscopy reveals polymorphous vessels including glomerular (yellow circle) and linear-looped (white circle) vessels, with a predominant peripheral distribution, within a pink-whitish background (white asterisk); scales and erosions are also observed (black arrow). F, Patient 8: Dermoscopy also reveals glomerular (yellow circle) and linear-looped (white circle) vessels, pink-whitish homogeneous areas (white asterisk), and associated scales and crusts [Colour figure can be viewed at wileyonlinelibrary.com]

Although histopathology complemented by genetic testing are long considered gold standard for the diagnosis of HHD, emergent noninvasive techniques, including dermoscopy and reflectance confocal microscopy (RCM), may also play an important role. Dermoscopy of HHD has been described in only two patients,[13,14] while its RCM features were also presented in one case series of four patients and in three isolated reports.[14-17] Herein, the aim of our study was to further characterize both dermoscopic and RCM features in HHD with histological correlation.

2 | MATERIAL AND METHODS

Eight patients with newly biopsy-proven HHD were consecutively recruited in two European Dermatology Clinics (Department of Dermatology of the Medical University of Graz, Austria, and Department of Dermatology of the Hospital de Santa Maria, University of Lisbon, Portugal). All patients were examined using dermoscopy and RCM, if feasible, with assessment of multiple lesions in each patient.

Dermoscopic pictures were taken using a 4-megapixel digital camera (Nikon Coopix 4500®, Nikon®, Melville, NY, USA) equipped with a contact, polarized dermoscope (DermLite® Photo 3Gen, San Juan Capistrano, CA, USA). Confocal images were obtained using a near-infrared, reflectance mode, confocal laser-scanning microscope (VivaScope 1500®, Caliber: imaging and diagnostics, Rochester, NY, USA). The confocal microscope was equipped with a diode laser of 830 nm and a digital dermoscopic camera (VivaCam®, Caliber:imaging and diagnostics, Rochester, NY, USA). In each case, a dermoscopic image was captured with the VivaCam® which showed precise correlation to the RCM mosaic images, and served as a map to guide RCM imaging through the lesion. A RCM mosaic ("VivaBlock" image) with a field of view of up to 8×8 mm was obtained when a sequence of individual images at a given depth was acquired and stitched together with a dedicated software. Three mosaics were obtained in all examined lesions at three different skin levels, from the stratum corneum to the upper dermis. Furthermore, several images (0.5×0.5 mm) were collected at an increasing depth according to the VivaStack modality.[18] All images were reviewed by experienced clinicians.

3 | RESULTS

A total of eight patients (four male and four female patients) with a mean age of 44 years (range 27-55) were observed. The diagnosis of HHD was confirmed by histological examination in all patients according to the presence of suprabasilar acantholysis with

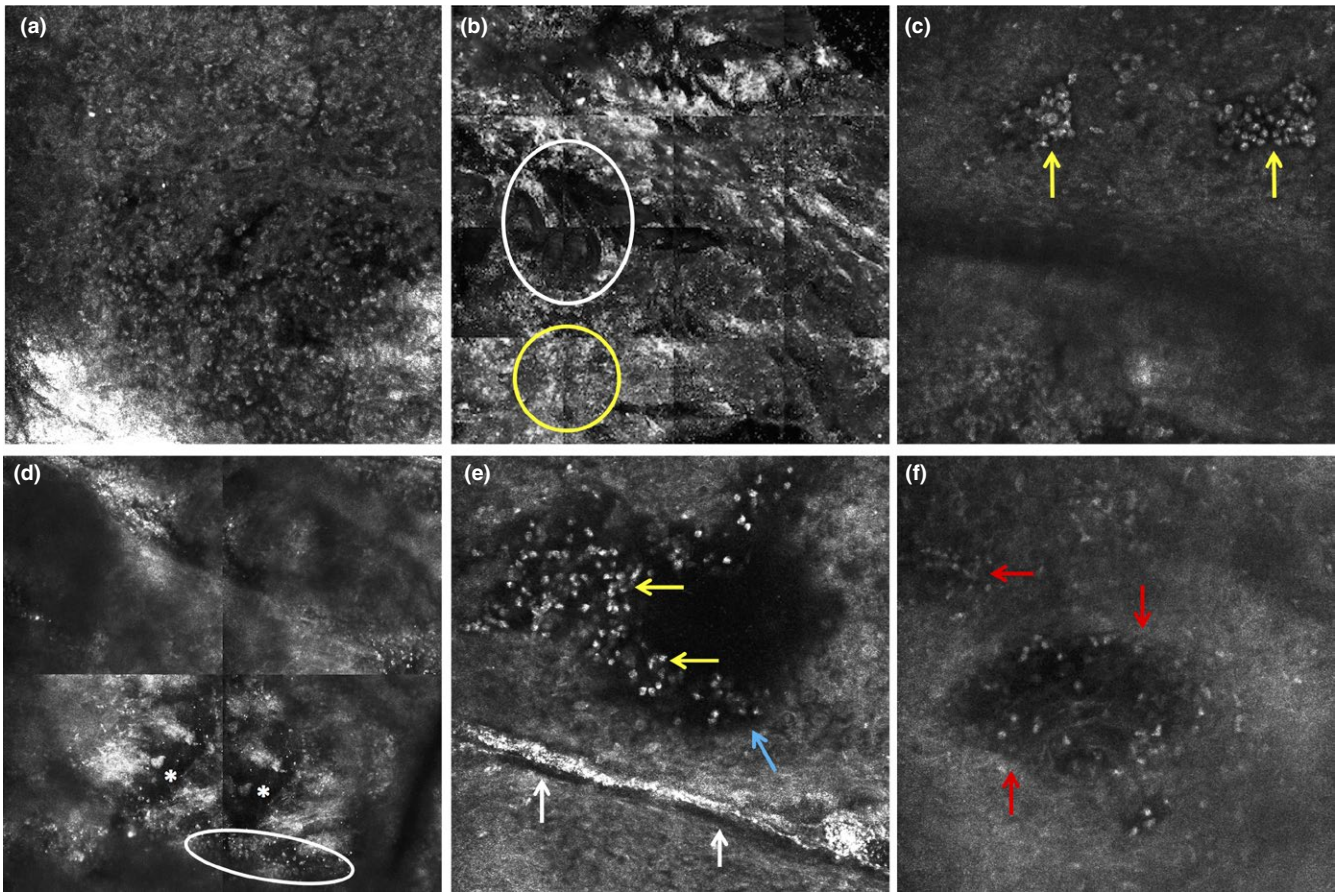

FIGURE 2 Reflectance confocal microscopic presentation in Hailey-Hailey disease: Patient 8 (lumbar region). A) Basic image, 0.5×0.5 mm: partial acantholysis with dilapidated brick wall appearance and disarranged epidermal pattern are observed at spinous and granular layer. B, Mosaic image, 2×2 mm: widened epidermal partial acantholysis (white circle) and infiltration of inflammatory cells (yellow circle). C, Basic image, 0.5×0.5 mm: dyskeratosis (yellow arrows) is observed as clustered bright oval structures corresponding to keratinocytes bellow the stratum corneum. D, Mosaic image, 1×1 mm: partial acantholysis (white circle), epidermal disarray, and intraepidermal clefting (white asterisks) seen as dark spaces within the epidermis filled with few bright inflammatory cells. E, Basic image, 0.5×0.5 mm: intraepidermal vesicle (blue arrow) with dyskeratotic cells within (yellow arrows) and adnexal structure sparing (white arrows). F, Basic image, 0.5×0.5 mm: dilated papillae with tortuous vessels within (red arrows), and inflammatory cells (seen as round-to-polygonal highly refractive structures) are observed at dermal-epidermal junction [Colour figure can be viewed at wileyonlinelibrary.com]

intraepidermal blistering and negative DIF. Clinical, dermoscopic, and RCM characteristics of all studied patients are summarized in Table 1.

All patients were symptomatic, with skin lesions being either itchy or painful, and particularly worsened by mechanical trauma, sweating, and heat exposition. They were mostly located on the skin folds: axilla (6/8), groin (5/8), inframammary (2/8), and lateral aspect of the neck (1/8). Typical clinical presentation was also observed, consisting of circinate (7/8) or vegetating (3/8) plaques, flaccid vesicles on erythematous skin (4/8), superficial fissures or erosions (5/8), and associated yellowish scales and crusts (6/8). The lesions were relapsing and present for a mean of 10 years (range 1-20) possibly due to delayed diagnosis. The patients have been misdiagnosed and treated for such diverse skin diseases, including candidiasis, impetigo, eczema, and inverse psoriasis (Figure 1A-D).

Dermoscopy disclosed the following features: polymorphous vessels (8/8), including glomerular (8/8), linear-looped or "spiral" (8/8), and coiled (1/8) vessels, randomly arranged over a pink-whitish (6/8) or pink-yellowish (2/8) background, with a predominant peripheral distribution found in four of the patients (Figure 1E and 1F). Scales (6/8) and erosions (7/8) were also observed.

Further RCM examination was performed (Figures 2-5). Intraepidermal clefts or vesicles and partial acantholysis (similar to a "dilapidated brick wall"), disarranged epidermal pattern, crusts, hyperkeratosis, acanthosis, sparing of adnexal structures, and dilated papillae with tortuous vessels within were observed in all patients. Dyskeratosis (3/8), uplocated papillae (3/8), and epidermal (5/8) or dermal (5/8) inflammatory cells were additionally seen.

4 | DISCUSSION

Acantholytic skin disorders are a heterogeneous group presenting with overlapping clinical and histological features. In addition, the

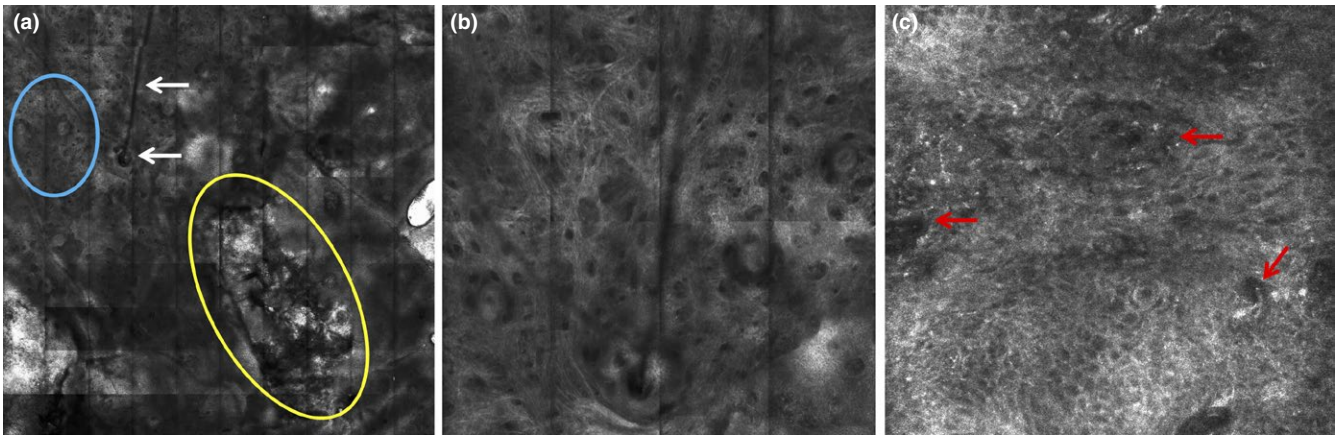

FIGURE 3 Reflectance confocal microscopic presentation in Hailey-Hailey disease: Patient 6 (axilla). A, Mosaic image, 5×5 mm: partial acantholysis (yellow circle), adnexal sparing (white arrows), and uplocated papillae (blue circle) are observed at epidermal level. B, Mosaic image, 2×2 mm: dilated papillae and tortuous vessels are observed at superficial dermis. C, Basic image, 0.5×0.5 mm: uplocated and dilated papillae with tortuous vessels (red arrows) within are observed at epidermal level [Colour figure can be viewed at wileyonlinelibrary.com]

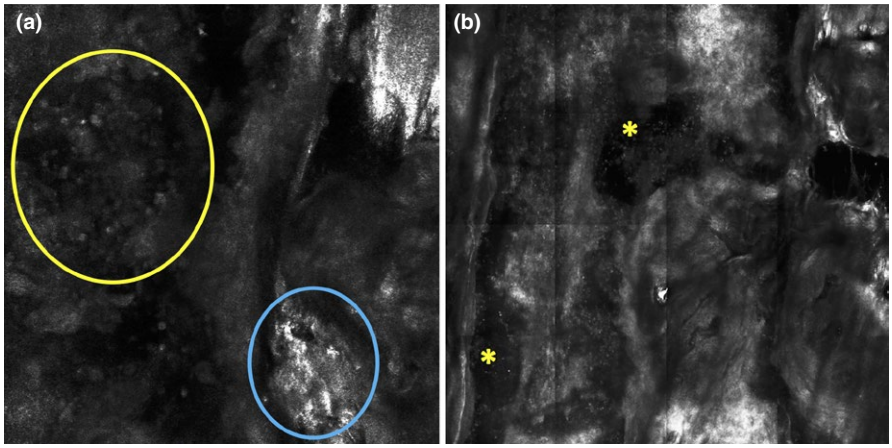

FIGURE 4 Reflectance confocal microscopic presentation in Hailey-Hailey disease: Patient 7 (axilla). A, Basic image, 0.5×0.5 mm: epidermal partial acantholysis (yellow circle) with dilapidated brick wall appearance and surface crusts (blue circle). B, Mosaic image, 2×2 mm: intraepidermal clefting or vesicles (yellow asterisks) filled with loose keratinocytes and inflammatory cells, and complete loss of epidermal pattern [Colour figure can be viewed at wileyonlinelibrary.com]

differential diagnosis of HHD might include other inflammatory and infectious skin disorders, particularly in clinically less obvious cases and in the absence of positive family history. The applicability of dermoscopy and RCM for the noninvasive diagnosis of inflammatory skin diseases have recently been recognized.[19-23]

Dermoscopic presentation of HHD has been described in two previous reports.[13,14] Its features included the combination of white and pink areas separated by pink furrows, resembling a cloud and an iceberg pattern, respectively. In our extended series, we found the same combination of white and pink colors. In addition, we found that under adequate clinical correlation, the identification of polymorphous vessels, glomerular, and linear-looped, within a pink-whitish background may be important dermoscopic clues for the diagnosis of HHD. Predominant peripheral vessel distribution was also identified in half of the patients. Absence of other features, such as central star-like pattern and "pseudocomedones," allowed the exclusion of other acantholytic diseases, like Grover disease and Darier disease, respectively.[24,25]

RCM findings were consistent to the few previously described cases.[14-17] Partial acantholysis similar to a dilapidated brick wall, intraepidermal clefting or vesicles, disarranged epidermal pattern, and crusts were found in all eight patients. Dyskeratosis was also observed in three patients. Its identification may be facilitated using RCM, being an in vivo technique. Dilated papillae with tortuous vessels within were also seen in all patients, which might be explained by the examination of long-lasting lesions. Uplocated papillae were also a unique feature of our study, seen as visible papillae at lower epidermal level. They are probably the result not only from lesion longevity but also from vili projections of dermal papillae protruding into epidermal blister cavities. RCM uplocated and dilated papillae with tortuous vessels correlate well to the dermoscopic observation of vascular polymorphism, including linear-looped and glomerular vessels, respectively. Epidermal inflammatory cells were observed in five patients, possibly due to secondary bacterial infection.[10,17]

Widespread acantholysis within the epidermis in HHD, resulting from intercellular bridge loss, is more pronounced than in Darier disease. Unlike Darier disease, where numerous corps ronds and grains can be found, dyskeratosis is mild and adnexal epithelium is spared. The later was a RCM feature seen in all our studied patients.

In conclusion, all RCM features had an excellent correlation to the classical histologic descriptors of HHD.

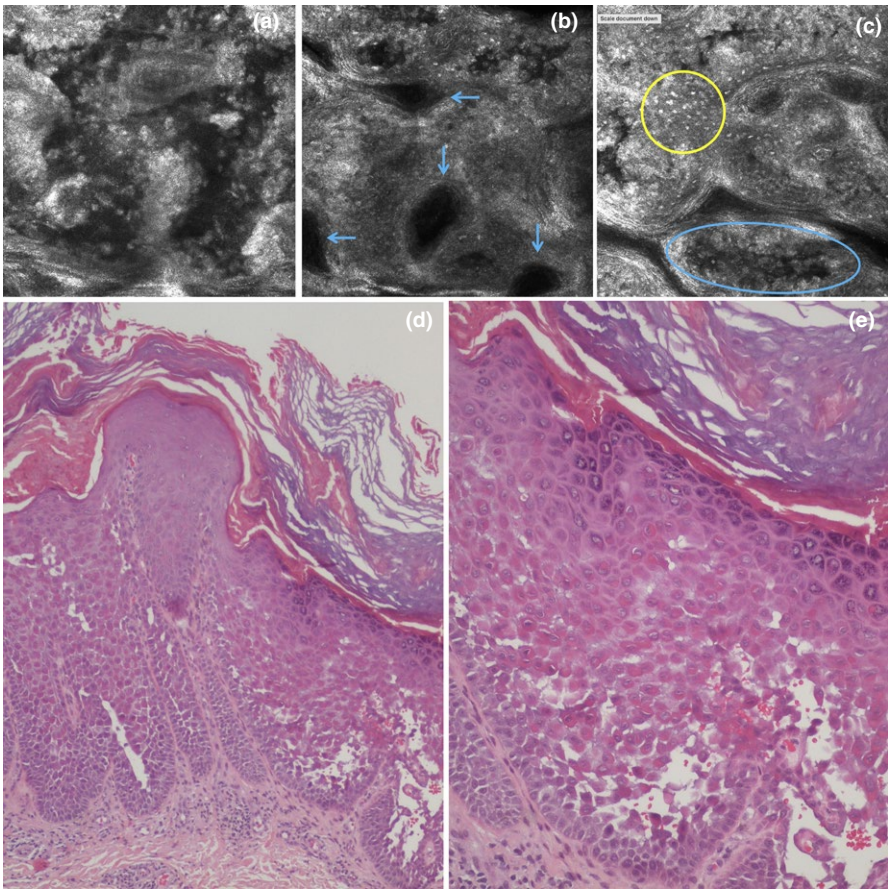

FIGURE 5 Reflectance confocal microscopic presentation with histologic correlation in Hailey-Hailey disease: Patient 1 (lateral aspect of the neck). A, Basic image, 0.5×0.5 mm: detail of partial acantholysis with dilapidated brick wall appearance observed at granular layer. B, Basic image, 0.5×0.5 mm: disarranged epidermal pattern and multiple vesicles (blue arrows). C, Basic image, 0.5×0.5 mm: dyskeratosis (yellow circle), epidermal disarray and partial acantholysis (blue circle). D, Hematoxylin-eosin staining, 100×: severe acantholysis with dyskeratosis and suprabasilar irregular clefting, regular acanthosis, focal hypergranulosis, and subjacent inflammatory infiltrate. E, Hematoxylin-eosin staining, 200×: detail of dilapidated brick wall appearance due to partial acantholysis and dyskeratosis, with an excellent correlation to the confocal findings [Colour figure can be viewed at wileyonlinelibrary.com]

Limited depth penetration to the superficial dermis is a known RCM limitation. Considering that most of pathologic abnormalities of HHD are found within the epidermis, RCM is of potential interest for its in vivo exploration and noninvasive diagnosis. Therefore, although definitive diagnosis was obtained by histopathology in all examined cases, RCM may allow early diagnosis of HHD and differentiation from other genodermatoses (including Darier disease) or more common fold inflammatory and infectious skin disorders. Hence, delayed diagnosis and wrong treatments or invasive diagnostic procedures among family members with similar phenotypic features could be avoided. In addition, it may contribute for early recognition of associated complications, common including infections (impetigo, eczema herpeticum), or rare including squamous cell carcinoma arising in previous HHD lesions.[26]

Recognition of the described dermoscopic and RCM features may be useful for the noninvasive response monitoring after treatment implementation in HHD recalcitrant cases, including ablative carbon dioxide laser, photodynamic therapy, dermabrasion, and botulinum toxin type-A injections.[27] In vivo observation of early subclinical changes can also be possible.

CONFLICTS OF INTEREST

The author has no conflict of interest.

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