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ORIGINAL RESEARCH

Dermoscopy as a Noninvasive Diagnostic Tool for Hailey-Hailey Disease and Darier Disease

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ABSTRACT

Introduction: Hailey-Hailey disease (HHD) and Darier disease (DD) are rare genetic disorders for which differential diagnosis, especially in less obvious cases, can be difficult. The diagnosis is based on the clinical picture and family history, and is confirmed by histopathologic examination. Dermoscopy is a noninvasive technique that is primarily used at the present time to diagnose skin cancers. However, in the past few years this technique has also been increasingly used as a noninvasive diagnostic tool of inflammatory skin diseases. The aim of the study was to evaluate whether dermoscopy is a useful noninvasive diagnostic tool for HHD and DD.

Methods: We performed an observational retrospective case series study involving 13 patients with HHD (n = 8) and DD (n = 5). The presence or absence of standardized dermoscopic features of inflammatory diseases (according to International Dermoscopy Society [IDS] guidelines) was assessed in these patients.

Results: The most distinctive feature of HHD was white clouds separated by pink furrows, visible in all cases (8/8; 100.0%). Another distinctive clue of HHD was the crumbled fabric pattern seen in six patients with HHD (6/8; 75.0%). These dermoscopic findings were not present in patients with DD. The most typical features of DD in the dermoscopic examination was star-like or oval-shaped yellow areas surrounded by whitish halo, visible in all patients (5/5; 100.0%). Another distinctive dermoscopic clue of DD was pinkish homogeneous structureless background, which was present in all patients (5/5, 100.0%). These latter two features were not observed in patients with HHD.

Conclusion: Dermoscopy reveals distinctive features of HHD and DD, respectively. Therefore, we conclude that dermoscopy can be an excellent complementary noninvasive tool in the diagnostic process of patients with HHD and DD.

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PLAIN LANGUAGE SUMMARY

Hailey-Hailey disease and Darier disease are rare genetic disorders, which are diagnosed based on the clinical picture and confirmed with skin biopsy. Dermoscopy is noninvasive diagnostic tool, which enables skin visualization at a 10-fold magnification. Currently, dermoscopy is mainly used to diagnose skin cancers. In the recent years, dermoscopy has been also increasingly used as a noninvasive diagnostic tool of inflammatory skin diseases. The aim of

the study was to assess whether demoscopy may be a useful tool in diagnosing Hailey-Hailey disease and Darier disease. The study included thirteen patients: eight with Hailey-Hailey disease and five with Darier disease. The most typical dermoscopic feature of Hailey-Hailey disease was white clouds separated by pink furrows, which were visible in all cases. Another distinctive clue was crumbled fabric pattern seen in 75.0% of patients with Hailey-Hailey disease. These dermoscopic findings were not present in patients with Darier disease. In dermoscopic examination the most typical feature of Darier disease was star-like or oval-shaped yellow areas surrounded by whitish halo, visible in all patients. Also, pinkish homogeneous structureless background was present in all patients with Darier disease. These features were not observed in patients with Hailey-Hailey disease. Dermoscopy reveals characteristic features of Hailey-Hailey disease and Darier disease. Therefore, it can be an excellent complementary tool in the diagnostic process of patients with those diseases.

Keywords: Darier disease; Dermoscopy; Hailey-Hailey disease; Familial benign chronic pemphigus; Keratosis follicularis; Non-invasive diagnostic skin tools; Videodermoscopy

Key Summary Points

Why carry out this study?

Hailey-Hailey disease (HHD) and Darier disease (DD) are rare genetic disorders, which are diagnosed based on the clinical picture, family history and confirmed with histopathologic examination. Dermoscopy is a noninvasive diagnostic tool, which is increasingly used in diagnosing of inflammatory skin diseases. The aim of the study was to evaluate whether demoscopy may be a useful as a noninvasive diagnostic tool of HHD and DD.

What was learned from the study?

The most characteristic dermoscopic features of HHD were the white clouds separated by the pink furrows and the crumbled fabric pattern. While in patients with DD the most typical dermoscopic features were the star-like or oval-shaped yellow areas surrounded by the whitish halo and pinkish homogeneous structureless background. Therefore, dermoscopy can be an excellent complementary diagnostic tool in patients with HHD and DD.

INTRODUCTION

Hailey-Hailey disease (HHD) or familial benign chronic pemphigus is a rare autosomal dominant genodermatosis caused by a mutation in the ATP2C1 gene encoding calcium and manganese pump (secretory pathway Ca^{2+}-ATPase pump type 1; SPCA1) [1–4]. The primary clinical features of HHD include flaccid vesicles on the erythematous background, which are soon replaced by erosions, fissures, crusts, and macerated plaques localized in the intertriginous areas [5]. Histopathologically, HHD is characterized by incomplete acantholysis, which can be compared to a "dilapidated brick wall." The indirect and direct immunofluorescence tests are negative. To date, there is no "gold standard" of treatment, although many therapeutic options have been proposed [1, 6]. The topical treatment includes glucocorticosteroids, antibiotics, and calcineurin inhibitors. Refractory lesions may be treated with oral antibiotics, systemic glucocorticosteroids, or retinoids. Methotrexate or cyclosporine have been also successfully used in a recalcitrant form of the disease [4, 6].

Darier disease (DD) or keratosis follicularis is a rare genetic disorder that is inherited in an autosomal dominant pattern. The mutation responsible for DD is in the ATP2A2 gene, which encodes sarcoplasmic reticulum Ca^{2+}-

ATPase 2 (SERCA2) [7, 8]. Typical clinical signs of DD are hyperkeratotic papules and plaques usually localized on the face, scalp, chest, neck, and upper back. Histopathologic examination reveals suprabasal acantholysis at all levels of the epidermis, as well as dyskeratosis of the keratinocytes [9–11]. The indirect and direct immunofluorescence tests are negative. In patients with a mild form of the disease topical retinoids, glucocorticosteroids, and calcipotriol can be used [7], while patients with severe diseases or unresponsive to the topical treatment can be treated with systemic retinoids, such as isotretinoin and acitretin [12]. It also has been reported that cyclosporin is efficacious in the treatment of DD [13].

In the past few years, dermoscopy has become a useful noninvasive diagnostic tool of skin cancers [14, 15]. Recently, trichocopy (dermoscopy of scalp and hair) has also been widely applied for the diagnosis and therapeutic monitoring of hair loss and scalp diseases [16–18]. In addition to these applications, dermoscopy is increasingly being used to diagnose inflammatory skin disorders (inflammoscopy). By revealing morphological details invisible to the naked eye, dermoscopy is a bridge between clinical and histopathologic examination, thereby facilitating the assessment of the skin lesions in inflammatory skin diseases [19–23]. However, dermoscopy should be always the second step of a "two-step procedure", preceded by differential diagnosis based on the clinical picture. According to the guidelines of International Dermoscopy Society (IDS), five parameters should be evaluated in general dermatology: vessels (morphology and distribution), scale (color and distribution), follicular abnormalities, other structures (color and morphology), and specific clues [23].

The first description of a dermoscopic pattern of skin lesions of patients with HHD treated with a CO_2 laser was reported in 2014 [24]. However, only two isolated reports and two case series studies assessing dermoscopic features of HHD have been published in the intervening years [25–28]. In contrast, the dermoscopic features of DD were described for the first time by Vázquez-López et al. in 2004 [29], to be followed in recent years by more detailed descriptions of the dermoscopic pattern of DD [30, 31]. In 2016 Errichetti et al. also described the dermoscopic features of type 1 segmental DD [32].

The aim of the study was to evaluate whether demoscopy is a useful noninvasive diagnostic tool of HHD and DD.

METHODS

We conducted an observational retrospective case series study assessing the presence or absence of standardized dermoscopic features of inflammatory skin diseases in patients with HHD and DD. The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the International Ethical Guidelines by the Council for International Organizations of Medical Sciences. The study protocol and tools were reviewed and ethically approved by Bioethics Committee at the Medical University of Warsaw. Data were collected from the videodermoscopic images database in the Department of Dermatology at the Medical University of Warsaw.

The inclusion criteria were: (1) confirmed diagnosis of HHD and DD based on histopathologic examination along with negative direct and indirect immunofluorescence tests; (2) age > 18 years; and (3) high-quality clinical and videodermoscopic pictures with a complete clinical description. The exclusion criteria were :(1) topical or systemic treatment 1 month before videodermoscopy examination; and (2) coexistence of another dermatological disease.

The data were collected from January 2015 to November 2021.

Statistical Analysis

For statistical analysis, R programming language was used ® Foundation for Statistical Computing, Vienna, Austria; (https://www.R-project.org/). To compare the differences in dermoscopic features between patients with HHD and those with DD, we used the Chi-square (χ^2) test. The Fisher's exact test was performed if Cochran's conditions were not met. The statistical results were considered to be significant at $p < 0.05$.

Table 1 The prevalence and statistical significance of videodermoscopic features evaluated in patients with Hailey-Hailey disease and Darier disease

Dermoscopic features	HHD (n = 8 patients)	DD (n = 5 patients)	p
Dotted blood vessels	8/8; 100.0%	3/5; 60.0%	0.128
Linear curved blood vessels	6/8; 75.0%	5/5; 100.0%	0.487
Yellow scale	6/8; 75.0%	5/5; 100%	0.487
Diffuse	4/6; 66.4%	4/5; 80.0%	1.000
Peripheral	2/6; 33.3%	1/5; 20.0%	1.000
White dots surrounded by vessels	6/8; 75.0%	0/0; 100.0%	0.021*
White dots do not surrounded by vessels	0/0; 0.0%	4/5; 80.0%	0.007*
Pink structureless areas	8/8; 100.0%	3/5; 60.0%	0.128
White clouds separated by pink furrows	8/8; 100.0%	0/0; 100.0%	0.007*
Crumbled fabric pattern	7/8; 87.5%	0/0; 100.0%	0.005*
Yellowish area encircled with whitish halo	0/0; 0.0%	5/5; 100.0%	0.001*
Star-like shape	0/0; 0.0%	3/5; 60.0%	0.035*
Oval-like shape	0/0; 0.0%	2/5; 40.0%	0.128
Pinkish homogeneous structureless background	0/0; 0.0%	5/5; 100.0%	0.001*

Values are presented as a number of patients with dermoscopic feature/total number of patients with this disease; followed by the percentage

DD Darier disease, *HHD* Hailey-Hailey disease

*Statistically significant difference at $p < 0.05$ between patients with DD and those with HHD

RESULTS

A total of 13 patients (10 females, 3 males) were enrolled in the study, eight with HHD and five with DD. The mean age was 51.6 (range 42–66 years) years. Videodermoscopic images at 20-fold and 70-fold magnifications were taken using the Fotofinder Medicam 1000 (FotoFinder Systems GmbH, Birnbach, Germany). All lesions were assessed using standardized basic dermoscopic patterns of inflammatory diseases as in reference [23]. The determination of specific clues of HHD and DD were based on the pre-existing literature and the authors' own experience. The evaluated videodermoscopic features are outlined in Table 1.

In total we assessed 510 videodermoscopic images of skin lesions (318 in patients with HHD and 192 in patients with DD). The first feature analyzed was the morphology and distribution of blood vessels. All examined patients with HHD (8/8; 100.0%) had dotted blood vessels that were uniformly distributed in the lesional skin (Fig. 1a); also dotted vessels that were homogeneously scattered in the skin lesions were observed in patients with DD, but they were less common (3/5; 60.0%; $p > 0.05$). In addition to dotted vessels, linear curved blood vessels appeared in both groups of patients (Figs. 1b, 2b, c). Uniformly arranged linear curved blood vessels were more frequently visible in patients with DD (5/5; 100.0%) than in those with HHD (6/8; 75.0%), but the difference was not statistically significant ($p > 0.05$). The second assessed feature was the color and distribution of scale. Yellow scale (Figs. 1b–c, 3a) was present in six cases of HHD (6/8; 75.0%). In most of cases (4/6; 66.7%), scale was diffused (Fig. 1c) and covered the whole surface of the skin lesions; however, in two

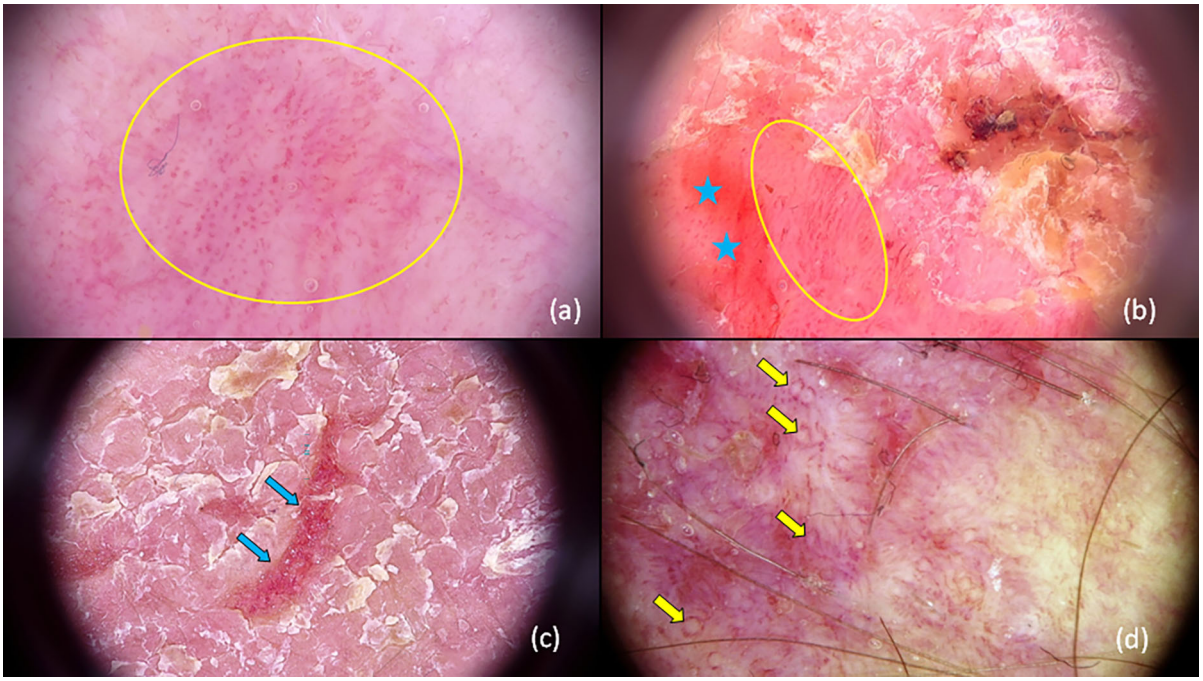

Fig. 1 Videodermoscopy of skin lesions in patients with HHD. **a** Dotted blood vessels (yellow circle) homogeneously scattered throughout the skin lesion (magnification ×20). **b** Pinkish homogeneous structureless area (blue stars) corresponding clinically to the erosion, linear curved blood vessels (yellow oval) uniformly distributed within the skin lesions, with yellowish scale localized mainly at the margin of the erosion (×20). **c** Diffused yellow scale covering the whole surface of the lesion; in the central part the pinkish structureless area can be observed (blue arrows) (×20). **d** White dots encircled by dotted blood vessels (yellow arrows). *HHD* Hailey-Hailey disease

cases (2/6; 33,3%) scale spared the center of the lesion and was distributed mainly at the margin (Figs. 1b, 3a). Peripheral scale appeared together with pink structureless areas that clinically corresponded to the erosions (Figs. 1b, 3a). In patients with DD, yellow scale (Fig. 2d) was present in all cases (5/5; 100.0%). In four of these patients (4/5; 80.0%) the scale covered the whole lesional skin (Fig. 2d) and in one case (1/5; 20.0%) the scale was on the edge of the pinkish area. The difference in the frequency of this feature between the DD and HDD groups was not statistically significant ($p > 0.05$). Follicle-associated dermoscopic features were not observed in either patient group. Another evaluated dermoscopic findings were structureless areas, dots or globules, lines and circles, which were classified according to their color and morphology. White dots were visible in patients with HHD and in those with DD; however, higher magnification disclosed that the white dots in patients with HHD were surrounded by a dotted blood vessel, while blood vessels around white dots were not observed in patients with DD. Regularly distributed white dots encircled by dotted blood vessels (Figs. 1d, 3a, c) were visible in six patients with HHD (6/8; 75.5%), but they were absent in patients with DD (0/0; 0.0%). While white dots not surrounded by blood vessels (Figs. 2a, 4c, d) were present in four cases of DD (4/5; 80.0%), they were not visible in any case of HHD. The difference in the incidence of this feature between these two groups was statistically significant ($p < 0.05$). The pink structureless areas were observed in all patients with HHD (8/8; 100.0%; Fig. 1b, c) and in only three patients with DD (3/5; 60.0%; Fig. 4d); the difference was not statistically significant ($p > 0.05$). During the analysis of videodermoscopic images of patients with HHD and DD we noticed specific clues strongly suggestive of the diagnosis. The most characteristic

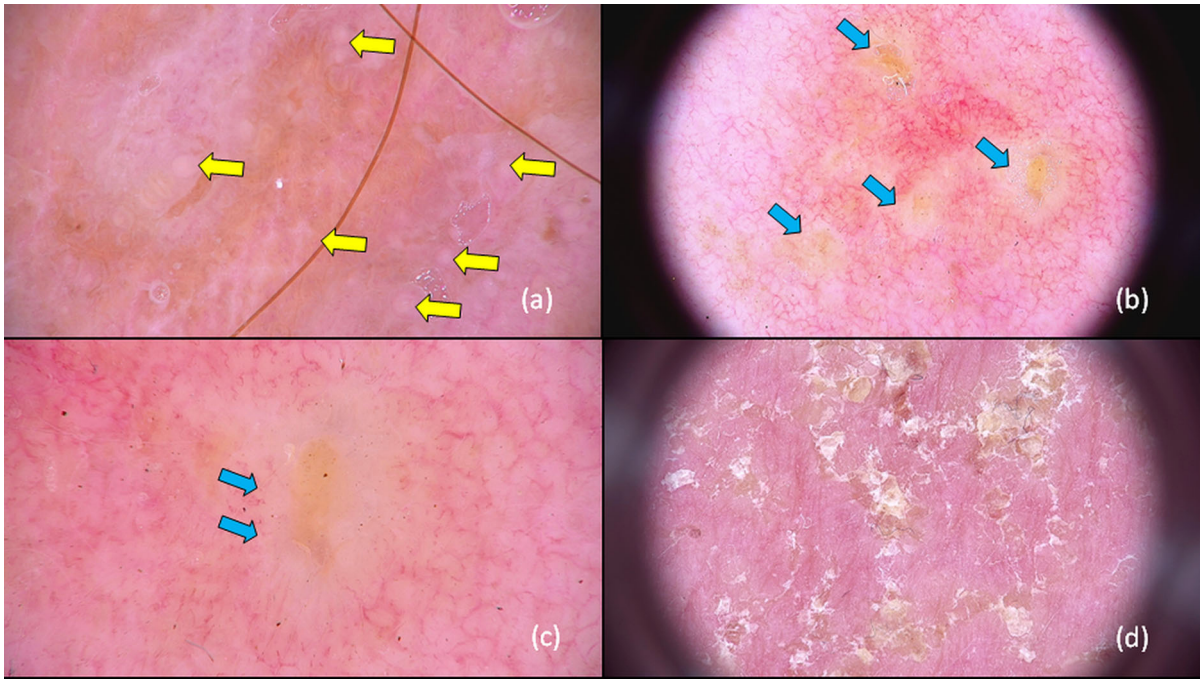

Fig. 2 Videodermoscopy of skin lesions in patients with DD. **a** White dots are not encircled by blood vessels (yellow arrows) (magnification ×70). **b** Uniformly arranged linear curved blood vessels and oval-shaped yellowish areas encircled with whitish halo (blue arrows) (×20). **c** Linear curved blood vessels around oval-shaped yellowish area surrounded by whitish halo (blue arrows) (×70). **d** Yellow scale covering the entire lesional skin, pinkish homogeneous structureless background (×20). *DD* Darier disease

clue for HHD were white clouds separated by pink furrows (Fig. 3d), which were present in all HHD cases in this study (8/8, 100.0%), but which were not observed in any patient with DD ($p < 0.05$). Another distinctive feature was crumbled fabric pattern (Fig. 3a, b), which was seen in seven patients with HHD (7/8; 87.5%) but not observed in patients with DD ($p < 0.05$). Also, in studying the videodermoscopic images of the skin lesions of patients with DD we found specific clues for this disease. In all cases (5/5; 100.0%) of patients with DD, star-like or oval-shaped yellow areas encircled by a whitish halo (Figs. 2b, c, 4a, b) were found; this feature was not observed in patients with HHD (statically significant difference at $p < 0.05$). Star-shaped yellow areas were visible in three cases of DD (3/5; 60.0%) and oval-shaped areas were visible in two cases (2/5; 40.0%). Also, a pinkish homogeneous structureless background was very characteristic for patients with DD, presenting in all five patients with DD (5/5, 100.0%); this background was not observed in patients with HHD (0/8; 0.0%; $p < 0.05$).

DISCUSSION

HHD and DD are rare genetic disorders, and the diagnosis, especially in less obvious cases, can be difficult [4, 9, 10]. Currently, the diagnosis is based on the clinical picture, family history, as well as on the histopathologic examination and immunofluorescence test results [4, 7, 10]. Interest is increasing in the possible application of dermoscopy and videodermoscopy in the diagnostic process of inflammatory skin diseases [20–23]. However, the dermoscopic pattern of HHD and DD has been described in only a few case reports and case series studies [24–33]. The aim of the present study was to assess whether dermoscopy could be a valuable noninvasive diagnostic method that can facilitate differential diagnosis of HHD and DD.

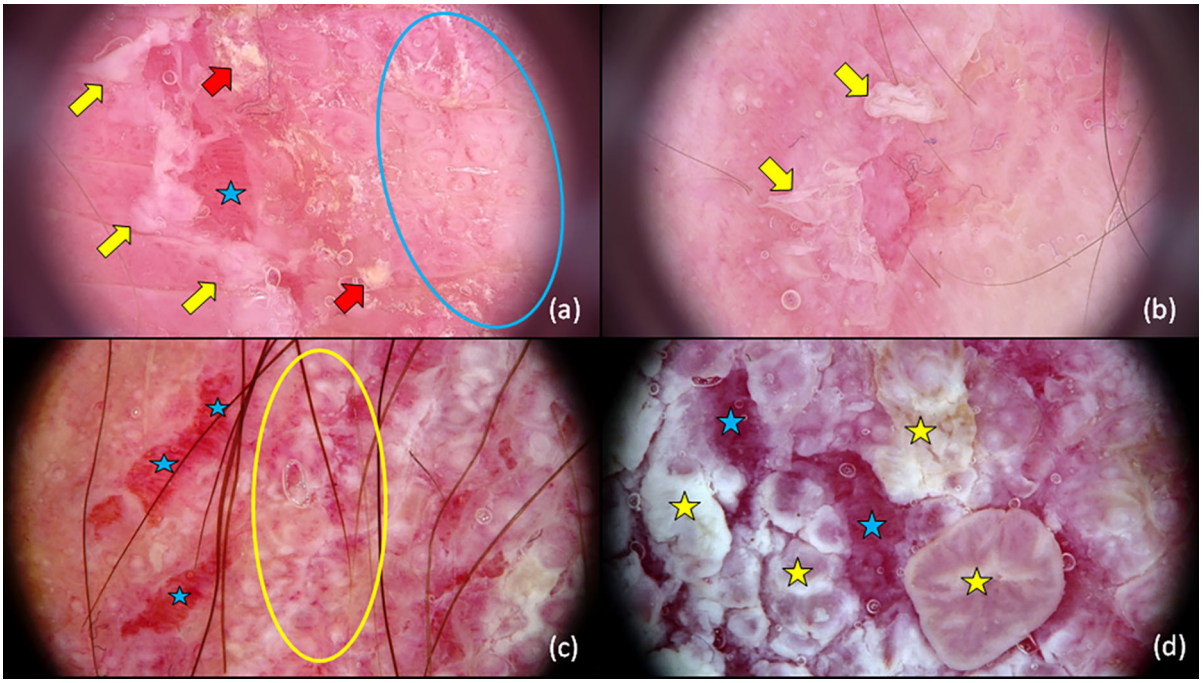

Fig. 3 Videodermoscopy of skin lesions in patients with HHD. **a** Pinkish structureless area (blue star) surrounded by the crumbled fabric pattern (yellow arrows) and the yellow scale (red arrows), as well as white dots encircled by dotted blood vessels (blue circle) (×20). **b** Crumbled fabric pattern (yellow arrows) (×20). **c** Pinkish homogeneous structureless areas clinically corresponding to the erosions (blue stars) and white dots encircled by blood vessels (yellow oval) (×20). **d** White clouds (yellow stars) separated by pink furrows (blue stars) (×20)

The most characteristic feature of HHD in presented study were white clouds separated by pink furrows. This observation is consistent with the findings of Kelati et al., who also described this feature in patients with HHD [25]. Ankad et al. described white gray structureless areas in HHD patients with dark skin in a multicenter observational controlled study [28]. Another specific feature that may be a helpful clue to distinguish HHD from other inflammatory and bullous disorders is the crumbled fabric pattern. This dermoscopic feature was described for the first time in a case report by Chauhan et al. in 2018 [26]. Dermoscopic images of our patients with HHD also revealed crumbled fabric pattern in most of the cases. To the best of our knowledge, this pattern has not determined in any other blistering disease. In patients with HHD, we also observed in all cases pink structureless areas that clinically corresponded to the erosions. Another characteristic feature was scale distributed at the margin of pink structureless areas. Erosions were also reported in the overwhelming number of patients with HHD (7/8) in the case series study conducted by Oliveira et al. and also in two case reports published earlier [25–27]. Ankad et al. also described in patients with HHD erosions (100.0%, 23/23), having in the most of cases a linear and parallel linear shape [28]. Another characteristic dermoscopic finding of HHD in our patients were white dots surrounded by dotted blood vessels. Again, to the best of our knowledge, this feature has not been reported in previous papers. Similar to our findings, dotted blood vessels were also described in earlier publications, but the distribution was slightly different [25–28]. Oliveira et al. delineates dotted blood vessels randomly arranged over a pink-whitish or pink-yellowish background, with a predominant peripheral distribution [27]. Ankad et al. reported the presence of dotted vessels in 95.6% (22/23) of patients with HHD, but in 56.5% (13/22) of

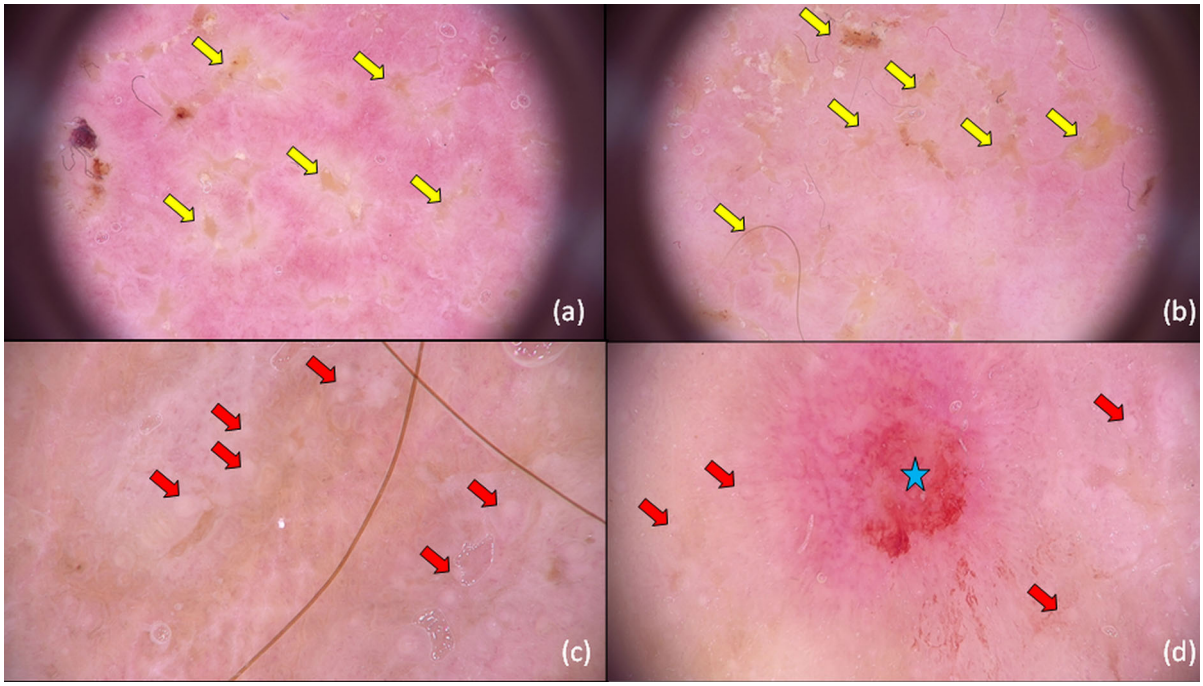

Fig. 4 Videodermoscopy of skin lesions in patients with DD. **a**, **b** Star-like yellow areas surrounded by whitish halo (yellow arrows) (magnification ×20). **c** White dots not surrounded by blood vessels uniformly distributed in the skin lesions (red arrows) (×70). **d** Pink structureless area (blue star) with extravasation encircled by the linear curved blood vessels and regularly scattered white dots (red arrows) (×70)

patients the distribution was clustered, and in 39.1% (9/22) the distribution was unspecific [28]. In our patients, dotted blood vessels were homogeneously distributed throughout the skin lesions. Videodermoscopy examination of a skin lesions of our patients with HHD revealed also the presence of linear curved blood vessels. The same observation has been reported in a previous case series [26, 27]. The yellow scale, which we found in most of our patients with HHD, was also described in previous studies published by Oliveira et al. and Ankad et al. [27, 28]. In other studies, the authors did not describe this finding.

In our study, the star-like or oval-shaped yellowish areas surrounded by a whitish halo were a distinctive dermoscopic feature of DD, which is consistent with the findings of most previous works [30–33]. However, in the first published study assessing the value of the handheld dermoscope in diagnosing DD, pseudocomedones were the most characteristic feature [29]. This structure was visible in dermoscopy as a dilated opening with raised or flat borders and a central brown or yellow hyperkeratotic plug. The difference between our study and the previous one may be related to the application of diverse dermoscopic techniques [29]. A central brownish or yellowish area surrounded by a whitish halo can also be visible in patients with Grover disease, especially in those with a histological Darier-like subtype [34, 35]. In our work, a pinkish homogeneous structureless background was found in all patients with DD, which is consistent with results reported in previous studies [30–32]. In 60.0% of our patients with DD, dermoscopy revealed the presence of dotted blood vessels; these results are comparable to those of earlier studies in which dotted blood vessels were also observed at a similar incidence [30–32]. In the present study, linear blood vessels were visible in all cases, while in a previous publication of Ericchetti et al. linear curved vessels were described in only four out of 11 patients with DD [31]. In another study, dermoscopy did not

reveal the presence of blood vessels in patients with DD and a brown to dark skin phototype [33]. Furthermore, the pink structureless areas were not present in a number of former studies, while in the present study we observed erosions in three cases [30–32]. Only in our study white dots have been reported in more than half of patients, although they were not surrounded by blood vessels, as in patients with HHD. The yellow scale was visible more frequently in our patients with DD (100.0%) than in previous studies [31, 33].

Dermoscopy can also be used to assess treatment response in patients with HHD and DD [24, 36]. There is one publication in the literature that evaluated CO_2 laser in patients with HHD using dermoscopy [24]. Also, there is one case report assessing dermoscopy as a tool for monitoring patients with DD during acitretin treatment [36]. These case reports showed that dermoscopy can be a useful method to evaluate treatment of HHD and DD; however, research with a larger study group is needed. In our study, we did not evaluate the effectiveness of treatment using dermoscopy.

To our knowledge, only a few publications have been published on this topic. We believe that presented study is a valuable addition to previous publications on this subject, as we assessed the presence or absence of standardized dermoscopic features of these inflammatory diseases according to IDS guidelines and compared their frequency with the frequencies reported in other available studies. Dermoscopy is an easily accessible diagnostic tool for dermatologists, and application of the findings reported here will enable a faster non-invasive diagnosis of HHD and DD.

The main limitation of the study was the small number of patients. Further studies are required to evaluate the repeatability of dermoscopic findings on a larger group of patients. Another limitation of present study was the lack of comparison of the dermoscopic features of HHD and DD with other vesiculobullous diseases.

CONCLUSIONS

In conclusion, dermoscopy is a useful noninvasive tool for diagnosing HHD and DD. The most characteristic dermoscopic features of HHD are white clouds separated by pink furrows, crumbled fabric pattern and white dots encircled by dotted blood vessels. In contrast, in patients with DD, dermoscopy shows star-like or oval-shaped yellow areas surrounded by whitish halo, pinkish homogeneous structureless background and white dots not encircled by dotted blood vessels. Based on these findings, we showed that dermoscopy can be an excellent complementary noninvasive tool in the diagnostic process of patients with HHD and DD.

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Author Contributions. All authors contributed to the study conception and design. Material preparation and data collection and analysis were performed by Marta Kurzeja and Adriana Rakowska. The first draft of the manuscript was written by Marta Kurzeja, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. The authors declare no conflict of interest.

Ethics approval. The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the

International Ethical Guidelines by the Council for International Organizations of Medical Sciences. The study protocol and tools were reviewed and ethically approved by Bioethics Committee at the Medical University of Warsaw. Informed consent was obtained from all subjects involved in the study for the publication of their cases.

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