Dermatology Practical & Conceptual

Dermoscopic Findings in Intraepidermal Carcinoma: an Interobserver Agreement Study

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Key words: intraepidermal carcinoma, squamous cell carcinoma in situ, Bowen's disease, dermoscopy, interobserver agreement

Citation: Fougelberg J, Luong A, Bowling J, et al. Dermoscopic findings in intraepidermal carcinoma: an interobserver agreement study. *Dermatol Pract Concept.* 2023;13(1):e2023114. DOI: https://doi.org/10.5826/dpc.1301a114

Accepted: January 12, 2023; **Published:** January 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: A wide range of descriptive terms have been used for dermoscopic findings in intraepidermal carcinoma (IEC) and the clinical diagnostic accuracy of IEC can be challenging. Furthermore, dermoscopic findings in IEC have only rarely been evaluated in fair-skinned populations.

Objectives: To measure the interobserver agreement between dermatologists for dermoscopic findings in IEC. Furthermore, to describe the frequency of these findings in a predominantly fair-skinned population.

Methods: One hundred dermoscopic images of histopathologically verified IECs were collected. The 11 most common dermoscopic findings described in previous studies were re-defined in a new terminology in a pre-study consensus meeting. Images were assessed by eight experienced international dermoscopists. The frequency of findings and the interobserver agreement was analyzed.

Results: Scales (83%), dotted/glomerular vessels (77%), pinkish-white areas (73%) and hemorrhage (46%) were the most commonly present dermoscopic findings. Pigmented structures were found in 32% and shiny white structures (follicular or stromal) in 54% of the IEC. Vascular structures (vessels and/or hemorrhage) could be seen in 89% of the lesions. Overall, the interobserver agreement for the respective dermoscopic findings was poor to moderate, with the highest kappa values noted for scales (0.55) and hemorrhage (0.54) and the lowest for pinkish-white areas (0.015).

Conclusion: Our results confirm those of previous studies on dermoscopy in IEC, including the frequency of pigmented structures despite the fair-skinned population. The interobserver agreement was relatively low. The proposed new terminology and our findings can hopefully serve as a guideline for researchers, teachers and students on how to identify IEC.

Introduction

Intraepidermal carcinoma (IEC), also known as Bowen's disease or cutaneous squamous cell carcinoma *in situ*, manifests clinically as a slow-growing, pinkish to brown plaque with scale and/or erosions, often occurring on chronically sun-exposed skin in the elderly. Histopathologically, IEC is characterized by atypical keratinocytes restricted to but spanning the full thickness of the epidermis [1].

Numerous dermoscopic findings in IEC have been described, including the presence of glomerular or dotted vessels, scales, erosions, erythema, white structureless areas, brown structureless pigmentation and brown dots in linear alignment [2-12]. Nevertheless, clinical diagnostic accuracy has been shown to be low in a previous study from our group [3], and several differential diagnoses, both benign and malignant, have been described to have similar dermoscopic findings [8, 12]. This may lead to unnecessary biopsies or inappropriate management. There is also a lack of studies exploring the interobserver agreement on the dermoscopic findings of IEC. Furthermore, dermoscopic findings in IEC have mainly been described in Southern European [3, 8-10], Asian [2, 4, 5] and Middle Eastern populations [7], and only rarely in predominantly fair-skinned populations [11, 12]. To be useful in a clinical setting and for teaching dermoscopy, a high level of interobserver agreement on dermoscopic findings in IEC is advisable. Knowledge regarding the level of interobserver agreement can also be used to refine the core teaching methods to identify IEC. Finally, evaluation of the prevalence of pigmented and non-pigmented dermoscopic structures in IEC in fair-skinned populations would be valuable in a clinical setting.

Objectives

In this study, we aimed to measure the interobserver agreement between dermatologists for identification of predefined dermoscopic findings in IEC. Furthermore, we aimed to describe the presence of these findings in a predominantly fair-skinned population, and possibly identify new diagnostic criteria to help identify IEC.

Methods

This retrospective, cross-sectional study of dermoscopic findings in IEC was performed at Sahlgrenska University Hospital in Gothenburg, Sweden, between September 1, 2020 and November 30, 2021. Dermoscopic image data were collected from a separate study cohort focusing on treatment of IEC. This cohort mainly consisted of patients with predominantly skin types I-III, although skin type was not consistently reported. One hundred dermoscopic images of histopathologically verified IECs were collected prospectively and consecutively from this study cohort. Dermoscopic images were taken with an iPhone 8 (Apple, Cupertino, California, USA) using a Dermlite DL4 dermoscope (DermLite LLC, Capistrano, California, USA) in polarizing mode. Unfocused images and images not showing the entire lesion were excluded. All dermoscopic images as presented to the dermatologists (readers) are made available in the supplementary material (Appendix S1). The study was approved by the Regional ethical review board in Gothenburg (approval number 283-18).

Based on the results from previous publications on the dermoscopic findings of IEC [2-6, 9, 10], the 11 most commonly described findings were selected and re-defined in a pre-study consensus meeting (Table 1). Eight readers from Sweden, Italy, Greece, United Kingdom, U.S.A., Argentina, Japan and Australia were invited to participate in the consensus meeting and subsequent image analysis. All readers had >10 years of experience of dermoscopy use. During the consensus meeting, 20 dermoscopic images of IEC (not included in the study dataset) were assessed and discussed until consensus was reached regarding the final list of dermoscopic findings and their definitions (Table 2). The previously described findings of "erosions", "ulceration" and/or "blood spots" were grouped and named "hemorrhage". "Erythema", "white structureless areas" and "hypopigmented (pink, skin-colored or white) structureless areas" were also clustered into the term "pinkish-white areas". "Shiny white structures" were divided into stromal (shiny white lines, blotches and/or strands) and follicular (rosettes

Table 1. Frequencies of the Pre-defined Dermoscopic Findings in Intraepidermal Carcinoma as Described in Previous Studies.

Dermoscopic category	Pre-defined dermoscopic finding	Previous studies							
		Papageorgiou et al. (2018) n=89	Yang et al. (2017) n=146	Payapvipapong et al. (2015) n=52	Ertop Dogan et al. (2021) n=34	Mun et al. (2009) n=26	Zalaudek et al. (2004) n=21	Cameron et al (2021) n≈52	Pan et al. (2008) n≈50
Vascular structures	Glomerular vessels	Dotted 60.7%, glomerular 60.7%	Glomerular 69.2%	Glomerular 94%, dotted 64%	Coiled 79.4%, dotted 20.6%	Glomerular 77%, dotted 12%	Glomerular 90%	Coiled vessels 44.2%, vessels arranged in clusters 5.8%	Glomerular 60%, red globules 32%, red globular rings 2%, red dots 60%
	Hairpin vessels	Hairpin (tortuous/ looped vessels) 15.7%		Hairpin 42%	Lo oped 14.7%				Hairpin 36%
	Linear vessels	Short fine telangiectasia 31.5%, arborizing 1.1%	Linear irregular 42.5%		Straight 2.9%, curved 2.9%, serpentine 11.8%, helical 2.9%	Linear irregular 12%, polymorphous/ atypical 8%		Vessels arranged in linear fashion 11.5%,	Arborizing 6%, atypical red 54%, comma 22%, corkscrew 10%
	Hemorrhage	Erosions 34.8%, large ulcerations/ bleeding 38.2%	Ulceration 15.1%, focal hemorrhages 55.5%	Ulcer 6%	Erosions 17.6%, ulcerations 26.5%, blood spots 32.4%	Ulceration 19%	Ulceration 28.6%		Hemorrhage, ulceration 44%
Keratin-related structures	Scales (white or yellow)	White 56.2%, yellow 41.6%	Scaly surface 78.8%, yellow crusts 56.8%, cotton candy sign 6.8%	Scaling 94%	Scales 58.8%	Scales 92%	Scales 90%		Hyperkeratosis 48%
	Keratin rim		Double-edge sign 30.1%						
Pigmented structures	Structureless brown pigmentation		Clusters of brown structureless areas 38.4%, homogenous pigmentation 34.9%	Structureless pigmentation 33%	Brown structureless pigmentation 29.4%	Structureless (homogenous) pigmentation 27%	Structureless (homogenous) pigmentation 80%		
	Brown-gray dots	Brown dots arranged in peripheral lines 9.0%, brown dots scattered 28.1%, blue-gray dots/globules 1.1%	Gray granules 39.7%, peripheral radial streaks 34.9%, brown dots/globules 28.8%	Pigment streaks 6%, pigment network 4% gray dots/globules 23%	Brown dots 5.9%, linear arranged dots 5.9%	Brown globules 31%, black globules 11.5%	Brown globules 90%	Brown or gray dots arranged in a linear fashion 21.2%	Blue-gray ovoid nests 6%, brown dots/globules 4%, negative pigment network 8%
	Pinkish-white areas		pseudonetwork 9.6%	Pinkish-white network 77%	Erythema 85.3%, white structureless 20.6%			Hypopigmented (pink, skin-colored or white) structureless zone 67.3%	Milky pink 8%, light pink 62%, dull pink 8%, light red 22%
Shiny white structures	Stromal structures		Focal/multifocal hypopigmentation 44.5%		White clods 11.8%				
	Follicular structures	White shiny blotches and strands 9.0%			White circles 14.7%, four-dot-clods 14.7%				

Table 2. Definitions of the dermoscopic findings.

Dermoscopic category	Pre-defined dermoscopic finding	Definition
Vascular structures	Glomerular vessels	Dotted/glomerular/coiled vessels (clustered, linear or diffuse)
	Hairpin vessels	Hairpin/looped vessels
	Linear vessels	Thin linear and/or branched vessels
	Hemorrhage	Erosions, ulceration and/or blood spots
Keratin-related structures	Scales	White and/or yellow scales
	Keratin rim	Peripheral rim of keratin as would be expected in typical cases of porokeratosis; no other peripheral scaling
Pigmented structures	Pinkish-white areas	Pinkish and/or white areas
	Brown pigmented areas	Areas with brown pigmentation
	Brown-gray dots	Brown or gray dots or globules
Shiny white structures	Stromal structures	Shiny white lines, blotches and/or strands
	Follicular structures	Rosettes or white circles

or white circles) structures. All dermoscopic findings were noted as present regardless of size, number, and distribution with the exception of the item "keratin rim" which inherently is distributed at the border of the lesion. Each dermoscopic finding was marked as present or absent. If further unlisted but relevant dermoscopic findings were identified, the readers were requested to specify these separately. The anonymized outcome from each reader is available as supplementary material (Appendix S2).

Statistics

The interobserver agreement for each dermoscopic finding was calculated using Fleiss' Kappa. The resulting Kappa values were interpreted as: poor (≤0), slight (>0 to 0.20), fair (>0.2 to 0.4), moderate (>0.4 to 0.6), substantial (>0.6 to 0.8) or almost perfect (>0.8) agreement. In addition, Fisher's exact test was used to compare the frequency distribution of the dermoscopic findings. All data were analyzed using R version 3.5.3.

Results

Images of 100 IECs in 94 patients (43 females [46%]) were included. The median age of the patients was 73 years (range 52-87 years). The most common tumor location was the head and neck area (43%) followed by the trunk (17%), upper limbs (24%) and lower limbs (16%). The median surface diameter of the lesion was 13 mm (range: 5–30 mm).

The frequencies of the dermoscopic findings and the interobserver agreements are summarized in Table 3 and examples are demonstrated in Figure 1. No new dermoscopic findings were described by any of the readers. The most commonly present dermoscopic findings were scales (83%), dotted/glomerular vessels (77%) and pinkish-white areas (73%). Among these, there was moderate agreement between readers for scales (κ=0.55), fair agreement for dotted/glomerular vessels (κ=0.32), but poor to slight agreement for pinkish-white areas (κ=0.02). Hemorrhage was present in almost half of the cases, showing a moderate interobserver agreement. Hairpin vessels and linear vessels were less frequently observed and demonstrated slight to fair interobserver agreement. Keratin rim was the least common finding, but showed a moderate interobserver agreement. Overall, pigmented structures, were shown in 32% of the cases, represented by brown pigmentation (19%) and brown-gray dots (26%) with fair interobserver agreement. Stromal shiny white structures were almost twice as common as follicular ones, and both demonstrated fair interobserver agreement. Shiny white structures overall were present in over half of the lesions (53%) with a fair to moderate agreement (κ=0.40). In 97% of all lesions, either glomerular/dotted vessels, scales or hemorrhage were present, (κ=0.41). Furthermore, almost all lesions (89%) showed vascular structures (vessels and/or hemorrhage) (κ=0.22). Figure 2 demonstrates the variation between readers for each dermoscopic finding.

Conclusions

In this retrospective, cross-sectional study of 100 dermoscopic images of IEC, we showed that scales, dotted/glomerular vessels, pinkish-white areas and hemorrhage were the most commonly present dermoscopic findings. Vascular structures could be seen in a majority of the lesions. Overall, the interobserver agreement for the respective dermoscopic findings was slight to moderate, with the highest kappa values noted for scales and hemorrhage.

Characteristic findings, generally regarded as predictive of IEC (scales, dotted/glomerular vessels, and hemorrhage)

Table 3. The frequencies of the dermoscopic findings in IEC and the interobserver agreement between the eight readers.

Dermoscopic finding	Frequency, % (95% CI)	Fleiss' kappa (95% CI)
Vascular structures		
Dotted/glomerular vessels	77.1 (74.1-79.9)	0.32 (0.29-0.36)
Hairpin vessels	26.4 (23.4-29.5)	0.14 (0.11-0.18)
Linear vessels	30.6 (27.5-33.9)	0.25 (0.22-0.29)
Hemorrhage	45.5 (42.1-49.0)	0.54 (0.50-0.57)
Keratin-related structures		
Scales	83.3 (80.5-85.7)	0.55 (0.52-0.59)
Keratin rim	3.4 (2.3-4.9)	0.44 (0.40-0.47)
Pigmented structures		
Brown pigmentation	25.8 (22.8-28.9)	0.37 (0.34-0.41)
Brown-gray dots	19.1 (16.5-22.0)	0.30 (0.27-0.34)
Pinkish-white areas	72.6 (69.4-75.6)	0.02 (-0.02-0.05)
Shiny white structures		
Stromal structures	42.8 (39.4-46.2)	0.39 (0.35-0.42)
Follicular structures	23.5 (20.7-26.6)	0.33 (0.30-0-37)

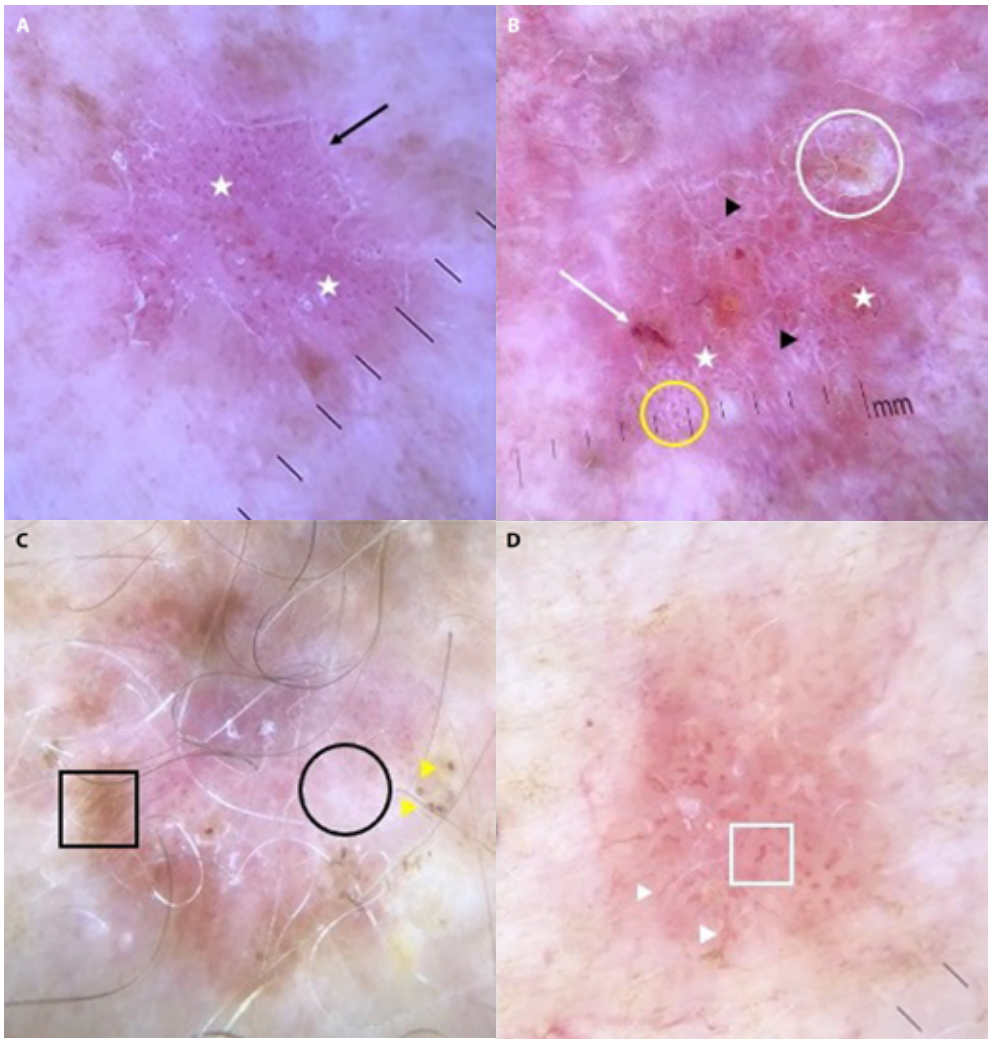

Figure 1. Images showing the 11 pre-definded dermoscopic findings used in the study: A) dotted/glomerular vessels (stars), keratin rim (black arrow); B) hemorrhage (white arrow), stromal structures (black arrowheads), dotted/glomerular vessels (stars), follicular structures (yellow circle); C) brown pigmented area (square), brown-gray dots (yellow arrowheads), pinkish-white area (black circle) and D) hairpin vessels (white circle) and linear vessels (white arrowhead).

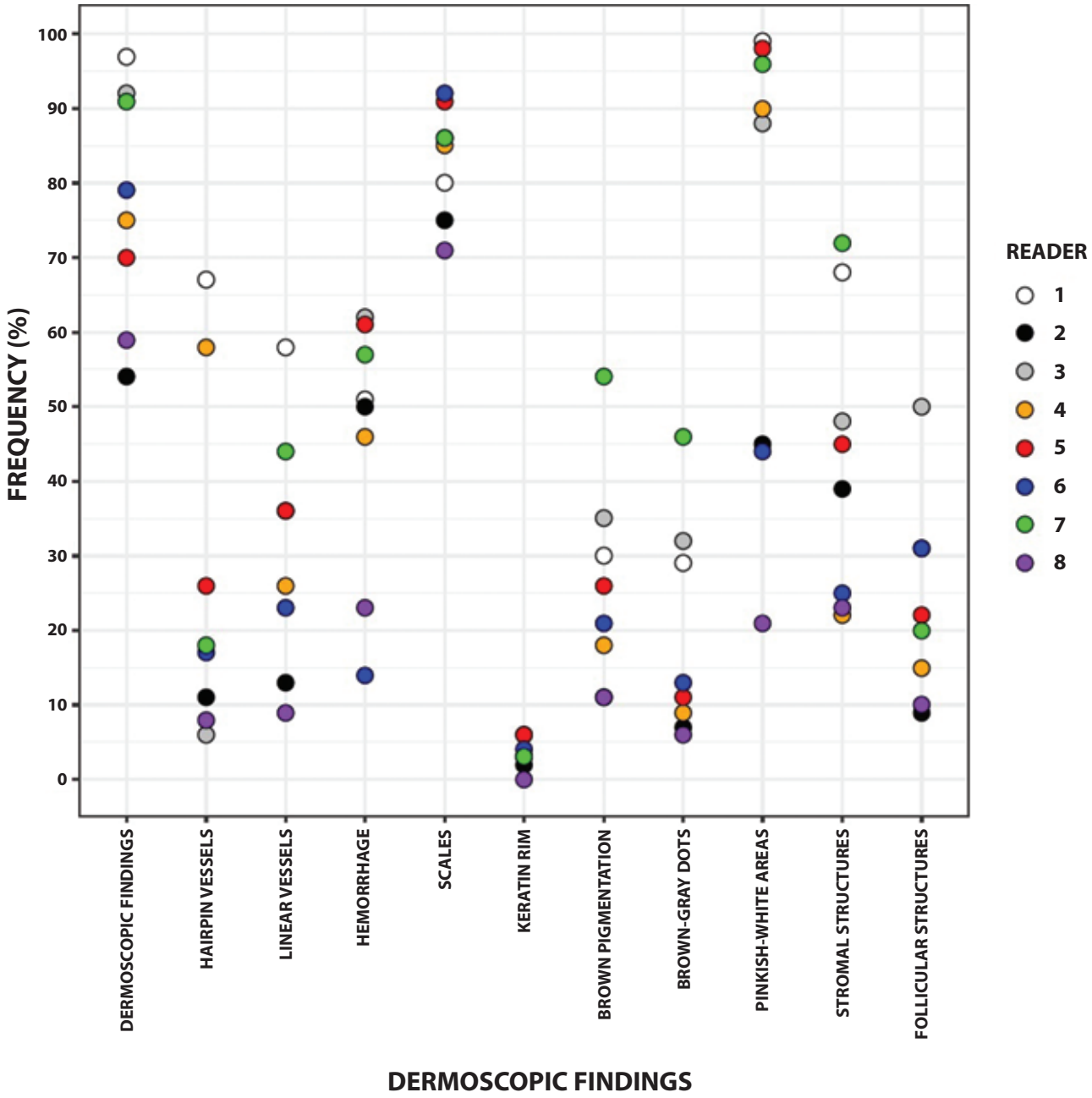

Figure 2. Scatter plot of the frequency of findings according to each reader.

were shown to be present at a similar frequency compared to previous studies [2-6, 9-12]. Scales and dotted/glomerular vessels were among the most common findings, present in four out of five lesions, with fair to moderate agreement. Previous studies have shown scales to be present in 48-92% [2-5, 7, 8, 12] and dotted/glomerular vessels to be present in 60-94% [2-7, 12]. Contrarily, Cameron *et al.* did not evaluate scales and showed a lower proportion of glomerular (coiled) vessels (44%), which may be due to only including pigmented IEC [11] [13].

The third most common dermoscopic finding in our cohort was pinkish-white areas which, however, showed a very low interobserver agreement. Pinkish-white areas have previously been described in a multitude of ways: pinkish-white network (77%) [4], erythema (85%) and white structureless areas (21%) [7]; hypopigmented (pink, skin colored or white) structureless zones (67%) [11]; and milky pink (8%), light pink (62%), dull pink (8%), and light red (22%) colors [12]. Despite having reached consensus over the definition of the dermoscopic finding of pinkish-white areas before the assessments, this finding seems to be difficult to interpret and should be interpreted with caution as a diagnostic marker for IEC. In fact, colors in general have been shown to be difficult to agree upon. Bajaj *et al.* showed that morphologic characteristics (*i.e.*, structures and patterns), not color, provide the primary diagnostic clue in dermoscopy [14].

The interobserver agreement on pigmented structures was fair and the overall frequency of these findings was

32%. This is similar to previously mentioned studies in which pigmented structures were observed in around 30% of IECs in cohorts from southern Europe, Asia and the Middle East [2-5, 7]. Taking into consideration that the population in our cohort predominantly was from the northern part of Europe with generally lighter skin types (I-III), 32% was higher than expected.

Over half of the lesions showed shiny white structures, either stromal or follicular, with a moderate interobserver agreement. Several previous publications have described such findings alternately as: shiny white blotches and strands, white clods, white circles or four dot clods [3, 7] (9-15%) and focal/multifocal hypopigmentation (45%) [5]. We believe that shiny white structures have the potential to be useful when describing dermoscopic findings in IEC in the future, given the relatively high frequency and moderate interobserver agreement.

Overall, the interobserver agreement for most dermoscopic findings ranged from poor to moderate. No finding had a higher agreement than κ=0.55 (scales), followed by κ=0.54 (hemorrhage). Although no other studies have examined the interobserver agreement for dermoscopic findings in IEC, a study on porokeratosis showed Kappa values that ranged from moderate to almost perfect for similar dermoscopic findings. For example, agreement was almost perfect for keratin rim, blood spots or erosions along the keratin rim, dotted or glomerular vessels and shiny white structures in porokeratosis [15]. Nevertheless, this study only included three readers from a single center, which may have contributed to the higher agreement.

Consensus on the dermoscopic terminology is important and intended to serve as a guideline for students, teachers, and researchers. Recently, the International Dermoscopy Society published a consensus agreement on descriptive and metaphoric terms for dermoscopic findings creating a helpful framework of standardized terms that allow for consistent use of dermoscopic terminology [16]. However, their list of terms did not include all the dermoscopic findings our group identified during our consensus meeting. Furthermore, the terminology used in previous publications on the dermoscopic findings in IEC have varied greatly [2-6, 9-12] Therefore, we proposed and defined a few new dermoscopic findings (*e.g.*, 'hemorrhage' and 'brown pigmented areas'). We also proposed a new grouping of shiny white structures into 'stromal' and 'follicular'. The keratin-related structures of 'scales' and 'keratin rim' which have been used to describe porokeratosis [15] were re-used here in an attempt to not introduce more new terms than necessary. Nevertheless, it remains to be shown whether our selected terms and definitions are the most appropriate considering the relatively low interobserver agreement on certain dermoscopic findings.

Strengths of our study include the relatively large number of lesions (n=100) in comparison to previous literature on dermoscopy in IEC, and that all lesions were histopathologically verified. Furthermore, all assessed images and the outcome from each dermoscopic reader are shared in supplementary files, which we believe is important for transparency in dermoscopy research. Although, the international group of readers ensured a diverse assessment, the high number of readers likely decreased the interobserver agreement. Further limitations include the lack of consistent reporting of skin types and the artificial setting without macroscopic images and/or clinical history. Furthermore, we did not include images of other keratinocytic tumors with similar dermoscopic findings. Also, we did not ask the readers to annotate the images to pinpoint the exact location of the observed dermoscopic findings.

Confirming previous publications, we found scales, dotted/glomerular vessels, and hemorrhage to be important dermoscopic findings in IEC with fair to moderate interobserver agreement. Interestingly, brown pigmented structures were more frequent than expected in a predominantly light-skinned population. This study also includes new terminology for dermoscopic findings in IEC, which require further evaluation. Future studies may also benefit from annotation of images to improve our understanding of the interobserver discordance, through directing the focus of the reader to specific areas within the lesion. Our results can hopefully be used to refine and improve the transfer of knowledge to new generations of dermoscopists on how to identify IEC. This could improve clinical diagnosis and enable more efficient lesion management by reducing the number of biopsies needed while still being able to make optimal treatment choices.

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