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Dermoscopy Research—An Update

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Dermoscopy increases the clinician's diagnostic accuracy by as much as 30% over that of unaided visual clinical inspection alone and has been confirmed in 3 separate evidence-based publications using a meta-analysis of the literature. It can be viewed as an in vivo bridge between clinical morphology and histopathology. This "bridge" has provided clinician researchers with many new insights into morphology and tumor biology. In this article, we provide the reader with an overview of the different aspects of dermoscopy as a research tool. We cover different aspects, such as the new equipment, new structures, the importance of blood vessels, etc.
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Dermoscopy increases the clinician's diagnostic accuracy by as much as 30% over that of unaided visual clinical inspection alone and has been confirmed in 3 separate evidence-based publications using a meta-analysis of the literature.[1-3] By tracking the number of dermoscopy units sold, it is clear that dermoscopy is gaining rapid acceptance worldwide by dermatologists and more recently by general practitioners as well (Millennium Research Group http://www.mrg.net). Dermoscopy can be viewed as an in vivo bridge between clinical morphology and histopathology. This "bridge" has provided clinician researchers with many new insights into morphology and tumor biology. In this article, we provide the reader with an overview of the different aspects of dermoscopy as a research tool.

Equipment

One of the reasons for the increasing popularity of dermoscopy is that new, easier-to-use instruments have become available. Since the first description of handheld dermoscopes in the 1980s, there have been important technological improvements. All second-generation devices have improved optics, use light emitting diodes for illumination, and allow for improved visualization of skin lesions. There are 2 main categories of dermoscopes available on the market: those using nonpolarized light (NPD) and those using polarized light (PD). NPD requires liquid immersion to visualize subsurface skin structures and PD does not. In a recent study by Benvenuto-Andrade et al, the authors investigated the differences between PD and NPD dermoscopy.[4] The authors concluded that PD and NPD did not provide equivalent information; however, the information gleamed from each dermoscope was in fact complementary. PD seems to offer a better visualization of structures located deeper in the skin, whereas immersion contact NPD allows for improved visualization of more superficial structures. For example, milia-like cysts can easily be identified under NPD (Fig. 1A) but are more difficult to impossible to visualize using PD (Fig. 1B). Other differences observed between NPD and PD was that granularity (peppering) is more clearly visualized with NPD. PD, by contrast, gave the observer more information pertaining to the lesion's vasculature and stroma (ie, collagen).

Structures

The Significance of Multiple Blue-Gray Dots (Granularity) for the Diagnosis of Melanoma

Based on the observation that the presence of multiple blue-gray dots within a pigmented neoplasm often prompts clinicians to biopsy the lesion led researchers to investigate the significance of this dermoscopic criterion for diagnosing melanoma.[5] The authors of 1 publication found that granularity was observed in 26.5% of all benign lesions and 93.5% of all melanomas (mainly in situ and early invasive melanomas). Granularity located at the periphery of the lesion, irregularly

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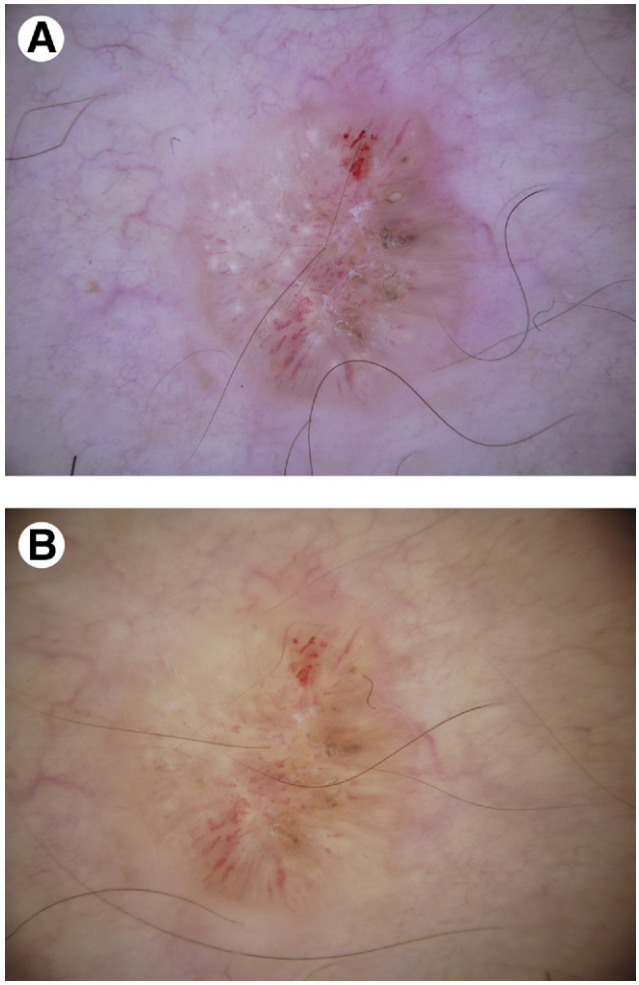

Figure 1 Milia-like cysts are better visualized using contact NPD (A) as compared to contact PD (B).

distributed granularity, and granularity in association with red or white colors were highly statistically significant for the diagnosis of melanoma (Fig. 2). It was also observed that granularity, if present, was mainly found in lesions located on sun-damaged skin. In the prospective part of their study, the

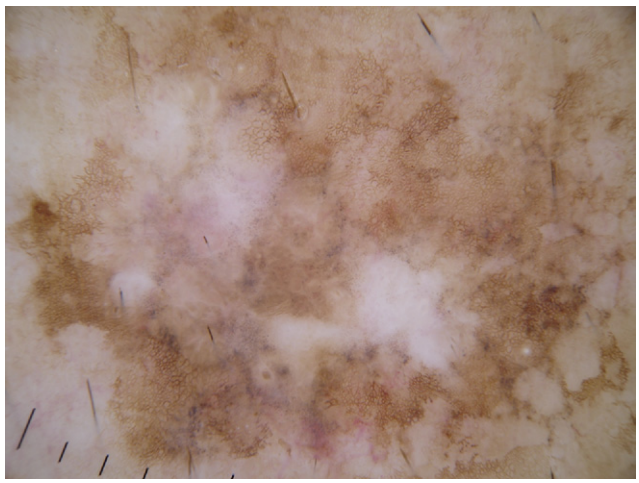

Figure 2 Granularity irregularly distributed in a melanoma on sun-damaged skin.

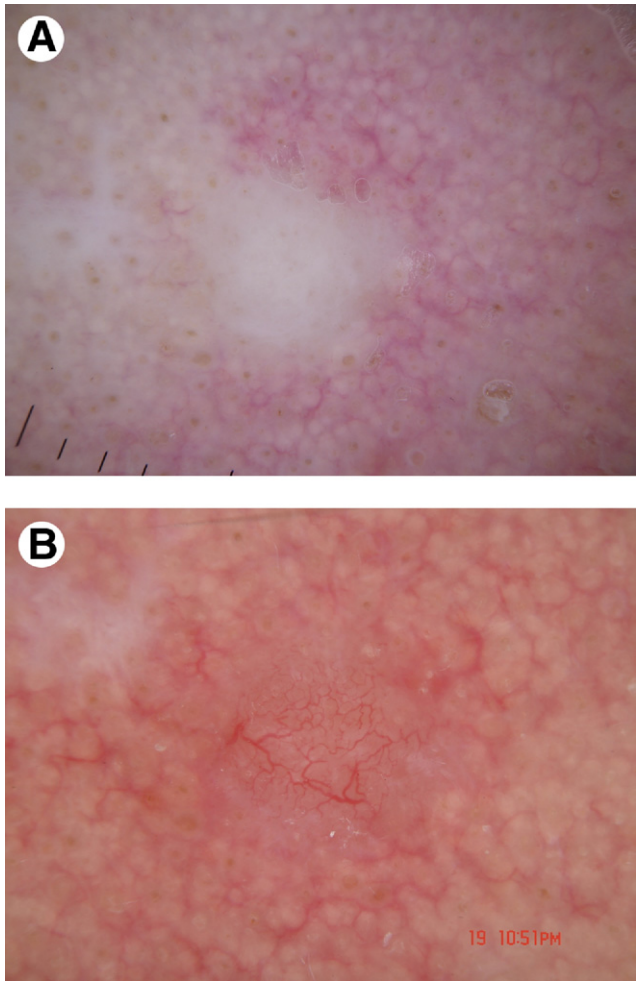

Figure 3 Contact NPD dermoscopy (A) causes blood vessels to blanch, whereas noncontact polarized dermoscopy (B) nicely reveals arborizing vessels in this basal cell carcinoma.

presence of granularity was calculated to have a sensitivity of 85% for the diagnosis of melanoma with a specificity of 99%. In conclusion, lesions with irregular granularity (ie, peripheral or irregularly distributed) should be biopsied, especially if the granularity is associated with the colors red, blue, or white. Lesions with a benign dermoscopy pattern, in which granularity takes on a uniform appearance and involves less than 10% of the lesion's surface area, are usually benign.

Significance of Vascular Structures

One of the advantages of using PD is that this technique negates the need of direct lesional contact, which, in turn, prevents applying pressure to the skin and causing blood vessels to blanch (Fig. 3A). In other words, noncontact PD facilitates improved visualization of blood vessels (Fig. 3B). The blood vessel morphology and vascular architecture have become important criteria for the diagnosis of a myriad of skin lesions, including both melanocytic (benign and malignant) and nonmelanocytic lesions.

Vascular Structures in Nonmelanocytic Tumors

- **Hairpin vessels** are U-shaped vascular loops, which at times may be twisted on themselves. In keratinizing tu-

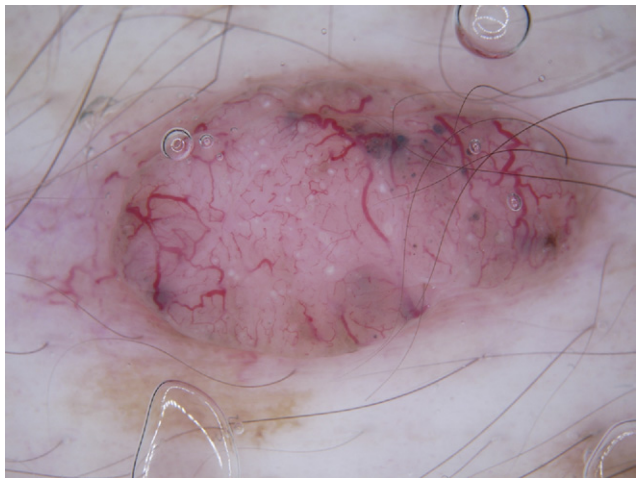

Figure 4 Nodular basal cell carcinoma with sharp in focus arborizing vessels.

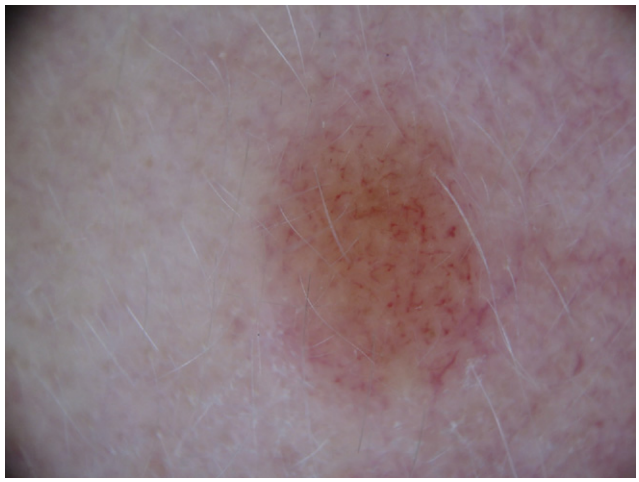

Figure 6 Comma vessels in an intradermal nevus.

mors, such as seborrheic keratoses and keratoacanthomas, the hairpin vessels are usually surrounded by a whitish halo.

- **Arborizing vessels** are vessels with a large diameter, branching irregularly into smaller and thinner diameter vessels. The vessels within the neoplasm appear bright red and in sharp focus (Figs. 3B and 4). They are frequently seen in basal cell carcinomas.
- **Glomerular vessels** are tortuous capillaries that resemble the glomerular apparatus of the kidney. These vessels are often distributed in clusters and are commonly seen in Bowen's disease (Fig. 5).
- **Crown vessels consist of linear or curved vessels, some of which may be arborizing,** located around the perimeter of a lesion. These vessels are directed toward the center of the lesion but they do not cross the lesion's center. Crown vessels are characteristically seen in sebaceous hyperplasia.
- **Dotted or glomerular vessels distributed in a serpiginous (ie, string of pearls) pattern.** This particular vascular architecture is the hallmark of clear cell acanthomas.

Vascular Structures in Melanocytic Tumors

- **Comma vessels** are slightly curved vessels that are commonly seen in dermal and compound melanocytic nevi (Fig. 6). In fact, the presence of regularly distributed comma vessels as the predominant vascular structure within a melanocytic tumor has been shown to be a negative predictor of melanoma.[6]
- **Dotted vessels** appear as tiny red dots. When present, they confer a positive-predictive value of 90% that the lesion is a melanocytic tumor.[7] The most common melanocytic tumor manifesting dotted vessels is melanoma (Fig. 7). However, dotted vessels can also be seen in dysplastic nevi, congenital nevi, and Spitz nevi.
- **Linear irregular vessels** are linear vascular structures of varying size and shape. They are characteristically associated with melanomas.
- **Polymorphous atypical vessels** represent a combination of 2 or more different types of vascular structures. The most frequent combination consists of linear irreg-

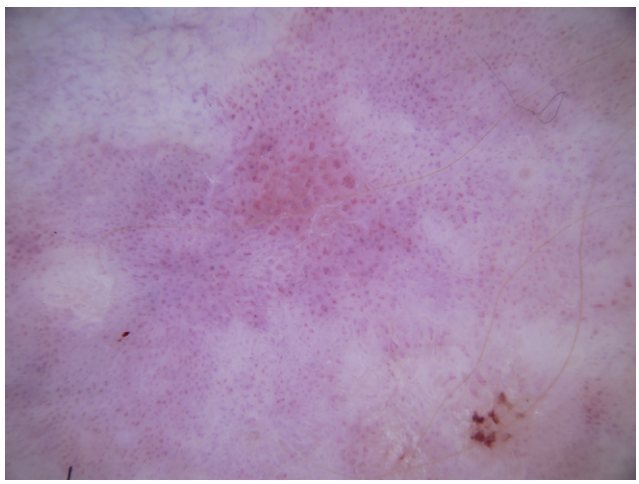

Figure 5 Glomerular vessels in a Morbus Bowen.

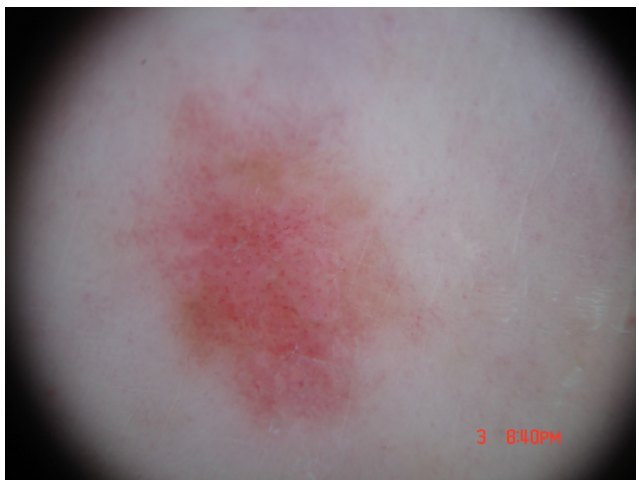

Figure 7 Dotted vessels in an amelanotic melanoma.

ular and dotted vessels. This particular combination of vessels, especially when they are predominantly located toward the center of the lesion, is highly indicative of melanoma.[6]

- **Atypical hairpin vessels** are serpentine-shaped vessels of varying size and shape. They are usually surrounded by a pink hue and will not have a surrounding whitish halo as commonly seen in keratinizing tumors.
- **Milky red globules** are reddish globules that are usually seen in association with areas of a milky red color. Their presence speaks in favor of an invasive melanoma.
- **Erythematous blush (also known as pink veil or milky red areas)** is a pinkish color or hue seen within a melanocytic tumor. The presence of more than 1 shade of pink is a positive predictor of melanoma.[6]

Significance of the Stroma

Analyzing lesions has revealed the presence of a newly-recognized dermoscopic structure called chrysalis. This so-called chrysalis structure consists of bright white orthogonal lines that can only be seen with PD. This structure is believed to correspond to an altered collagen stroma and it can commonly be seen in dermatofibromas, basal cell carcinomas, and scars. However, if it is seen within a melanocytic lesion, then it speaks in favor of a diagnosis of melanoma or Spitz nevus.[8,9]

The Complexity of Diagnosing Melanoma and What Dermoscopy Has Taught Us Regarding Image Recognition

Despite the best intentions of the examining clinician and despite the introduction of noninvasive diagnostic tools, such as dermoscopy, the clinician's diagnostic accuracy can never be 100%. Some melanomas may simply escape detection due to their small size, due to their lack of melanoma-specific morphologic features, and/or because they do not stand out as ugly ducklings. Furthermore, some melanomas may masquerade as benign neoplasms, such as seborrheic keratoses, thus making their detection extremely challenging. Minimizing the chance of misdiagnosing melanoma requires that we gain insights into some of the image recognition processes used by our eyes and brain during the performance of a physical examination of the skin. The examination can be divided in 2 different steps. In the first step, the entire skin surface is examined using saccade or scanning vision. During this process, all outlier or ugly duckling lesions are identified; hence, it is the main determinant of diagnostic sensitivity. In the second step, the clinician focuses on individual outlier lesions. During this process, the eye focuses on the lesion of interest and saccade eye movements are suppressed thus, allowing light to be focused on fovea. This in turn permits the clinician to evaluate the lesion while it is in sharp focus, which allows for the detection of subtleties in color, shape, contour, and topography that are essential for correctly differentiating benign from potentially malignant lesions. This second level relies on both pattern recognition and analytical analysis and it is the main determinant of the clinician's specificity. However, it is also important for us to acknowledge that our final decision regarding the diagnosis rendered for a given lesion is influenced by multiple factors, including the history of the patient, analytical evaluation (ie, clinical ABCD, dermoscopy criteria) of the lesion, differential recognition (ie, outlier lesion on the clinical or dermoscopic level), comparative recognition (ie, total body photography, short-term dermoscopic mole monitoring), gestalt or pattern recognition (clinical or dermoscopic level), and "gut feeling."

As mentioned above, even after a thorough examination some melanomas may be misdiagnosed. Awareness of the most common pitfalls in melanoma diagnosis may help in correctly identifying some melanomas that would otherwise have been misdiagnosed.

The Role of Dermoscopy in Avoiding the Misdiagnosis of Melanoma

The authors of a recent review article enumerated the most common pitfalls in the diagnosis of melanoma.[10] The 7 most common causes resulting in errors in diagnosing melanoma were as follows:

1. misdiagnosis of nodular melanoma as a benign lesion by the dermatologist.
2. misdiagnosis of nodular melanoma as a nevus by the pathologist.
3. incomplete biopsy leading to an inaccurate diagnosis.
4. melanoma misdiagnosed as a "dysplastic nevus involving margins."
5. melanoma misdiagnosed as Spitz nevus (by either the dermatologist or the dermatopathologist).
6. unrecognized desmoplastic melanoma (by either the dermatologist or the dermatopathologist).
7. patients presenting with metastatic melanoma with an unknown primary.

The authors of the above article also provided suggestions for clinicians regarding methods to help avoid or at least minimize the chance of misdiagnosing melanoma. In brief, there are 2 main areas that deserve reflection by the clinician. First, the clinician should always remember that the correct pathology diagnosis hinges to some extent on the type of biopsy performed. In should be intuitively obvious to clinicians that providing the pathologist with the entire specimen will ultimately result in the most accurate diagnosis. The ideal biopsy technique should encompass sampling the entire lesion. This may be accomplished via shave excision (ie, saucerization) or simple excision with a narrow margin. Second, many of the errors in diagnosis listed above can be minimized using dermoscopy. For example, clinically banal-appearing nodular or desmoplastic melanomas can correctly

be identified via dermoscopy. However, it is also important to remember that lesions manifesting a nonspecific dermoscopic morphology require close attention because a subgroup of melanomas fail to manifest any specific features. Argenziano and colleagues enumerated 7 clinical management rules, which they believe may prevent missing or misdiagnosing melanomas, especially those that fail to reveal any known dermoscopy specific criteria[11]:

1. dermoscopy should not be used only for clinically suspicious skin lesions.
2. biopsy all lesions that lack a clinical-dermoscopic correlation.
3. biopsy lesions with a nonspecific pigment pattern.
4. biopsy lesions with Spitzoid features.
5. biopsy lesions with features of extensive regression.
6. in patients with multiple nevi, biopsy lesions that reveal change during short-term follow-up.
7. biopsy pink lesions, especially those manifesting an atypical vascular pattern.

Sequential Digital Dermoscopy Imaging Helps Avoid Missing Featureless Melanomas

Digital imaging equipment and storage devices for the images are readily available and relatively inexpensive. This has allowed for their diffusion into routine clinical practice. Multiple researchers have published their findings regarding the effectiveness of short-term (3- to 4-month interval) sequential digital dermoscopy monitoring of lesions as a means of identifying "featureless" superficial spreading or lentigo maligna melanomas.[12-14] The reliance on sequential monitoring of flat featureless lesions as a means of identifying melanoma is based on the premise that benign lesions are generally biologically quiescent (ie, senescent) and therefore they usually do not reveal any changes on follow-up. In contrast, the majority of melanomas are biologically dynamic lesions and thus it is assumed that they will in fact manifest changes over time. With that being said, it is important to be cognizant of the fact that only flat lesions should be subjected to sequential monitoring, because superficial melanomas are known to grow slowly enough that a delay in their biopsy by a few months will not result in any harmful consequences. In contrast, nodular lesions should never be subjected to monitoring because they are reported to grow as rapidly as 0.5 mm in-depth per month. Sequential imaging research has also provided us with insights into the potential biology of some lesions. For example, sequential dermoscopy imaging has informed us that nevi with a peripheral rim of globules represents nevi that have not yet entered senescence. Thus, it can be anticipated that these lesions will enlarge during follow-up; eventually the peripheral rim of globules will disappear and then many of these nevi will enter into a senescent state.

Insights Into the Biology of Nevi and Melanoma

It is well documented that most dermoscopic structures have specific histopathology correlates. The ability to visualize subsurface structures within a lesion in vivo and infer its histopathologic appearance has provided researchers with many new insights into nevogenesis and melanoma genesis. For example, dermoscopic observations lend support to the theory that the different subtypes of melanoma are derived from stem cells located in different compartments of the skin.[15] Furthermore, these observations have also fueled new theories regarding the significance of remodeling of the Dermo-epidermal junction in melanoma.[9] In addition, sequential imaging has provided us with a new appreciation of the rate of growth of melanoma. While some melanomas, such as nodular melanomas, grow very rapidly, other melanomas grow at a rate that is so slow that they appear indolent. However, an area where dermoscopy has had the greatest impact is in questioning the dogma that nevogenesis occurs via the "Abtropfungs" theory as proposed by Unna. The observation that the most common nevus pattern in children is globular (ie, representing dermal or compound nevi) and in adults is reticular (ie, representing junctional or compound nevi) appears to negate Unna's theory, which states that nevi at their inception are junctional, subsequently evolving into compound nevi, before culminating their life cycle as intradermal nevi.[16-21] Longitudinal dermoscopy data have confirmed that the globular nevus pattern in children is more prevalent than is the reticular pattern.[19,22] The longitudinal dermoscopic follow-up of nevi in children via sequential digital monitoring has also revealed that individual nevus patterns remain relatively stable over time. In other words, it is extremely rare for a globular pattern nevus to transform into a reticular pattern and vice versa. All of these observations have lead to a new dual concept of nevogenesis theory: this theory purports that the presence of some nevi are determined in utero (ie, congenital) while others are acquired. The induction of acquired nevi may be related to environmental factors, such as ultraviolet exposure, and these nevi tend to manifest a reticular dermoscopic pattern. In contrast, the induction of congenital nevi appears to be related to events occurring during embryogenesis and these nevi tend to manifest a predominant globular pattern. Recent histopathology observations have documented the presence of incipient nevus nests in normal skin. This has also been confirmed by dermoscopy by observing small globules in normal-appearing skin of some children. These dermoscopic and histopathology observations suggest that the nidus for some nevi may be present in normal skin.

Nail Dermoscopy

The use of dermoscopy for examination of nail pigmentation was published by Ronger et al in 2002.[23] Recently, a review article on the diagnosis and management of nail pigmentation has been published providing a simplified diagnostic

algorithm.[24] Similar to dermoscopy of pigmented lesions, in the first step one has to determine if the nail pigmentation is of melanocytic or nonmelanocytic origin (blood or fungus). Melanonychia striata are tiny melanin granules (inclusions) of the nail plate visible with dermoscopy. In nail pigmentation of nonmelanocytic origin (nail hyperchromia), the pigmentation is homogeneous without the granular aspect corresponding to melanin inclusions in the nail plate.

Independent from the dermoscopy aspect, consider the following signs/symptoms:

1. any isolated pigmentation of a single digit that develops during the fourth to sixth decade of life.
2. any nail pigmentation that develops abruptly in a previously normal nail plate.
3. any changing pigmentation (pigmentation that becomes larger or blurred).
4. any subtle pigmentation of the thumb, index finger, or large toe.
5. any pigmentation in association with a history of digital trauma.
6. any new lesion in patients with a personal history of melanoma.
7. any nail pigmentation in association with nail dystrophy.
8. any nail pigmentation with the presence of a pigmentation of the periungual skin (Hutchinson's sign).

Dermoscopy of the Free Edge of the Nail Plate

Nail dermoscopy is usually limited to the examination of the nail plate by applying ultrasound gel between the curved nail plate and the dermoscopy contact plate. Prior to biopsy, it is important to know whether the pigmentation in melanonychia striata originates from the proximal or distal nail matrix.[25] It is known that a biopsy that includes the proximal nail matrix is likely to result in permanent nail dystrophy. A biopsy resulting in permanent nail dystrophy would be unavoidable if the lesion of concern is located in the proximal matrix. A biopsy performed of the distal nail matrix is less likely to result in significant nail dystrophy. Therefore, if the lesion is located in the distal matrix, the biopsy can be planned in such a manner as to avoid damaging the proximal matrix, thereby minimizing the resulting nail dystrophy. Histopathology examination of the distal nail clipping can help determine whether the origin of the pigment is in the proximal or distal nail matrix. However, a much easier, faster, and less-expensive method to attain the same information is using dermoscopy. Dermoscopy performed on the free edge of the nail can inform the clinician as to the origin of the pigmented nail band.[25] Due to the anatomy of the nail apparatus, pigmentation produced in the proximal nail matrix will appear in the upper portion of the free nail edge, whereas pigmentation originating from the distal nail matrix will appear as pigmentation in the lower part of the free nail edge.

Hair and Scalp Dermoscopy

The use of dermoscopy for the diagnosis of hair and scalp disorders appears to be quite promising. The authors of some recent publications did evaluate various hair and scalp disorders and discussed their specific dermoscopic findings.[26-29] It appears that the vascular patterns in scalp lesions may be helpful in correctly diagnosing different entities. Interfollicular simple red loops consisting of multiple, relatively evenly spaced, fine red lasso-shaped loops were identified in both normal and diseased scalps, but they were not seen in discoid lupus erythematosus, presumably because of epidermal atrophy. Interfollicular twisted red loops, consisting of relatively evenly spaced, twisted red loops, were associated with psoriasis and folliculitis decalvans. They were rarely seen in seborrheic dermatitis. These simple and twisted loops seem to correspond to capillary loops in the dermal papillae. Besides vascular structures, the presence of "yellow dots" appears to be a prominent dermoscopic feature of alopecia areata. The presence of yellow dots may allow clinicians to differentiate alopecia areata from trichotillomania or telogen effluvium. These yellow dots are thought to represent degenerated follicular keratinocytes and sebum within the follicles. In addition, hair shaft anomalies found in alopecia areata, such as "cadaverized hairs," "exclamation mark" hairs, and dystrophic hairs can readily be seen with the help of dermoscopy.

Conclusion

Dermoscopy is a method that improves the diagnostic accuracy of clinicians. At the same time, it has enabled us to better appreciate the morphology and tumor biology of different lesions. Furthermore, it has fueled new insights into nevogenesis and melanoma genesis. Dermoscopy will surely continue to evolve as an important research tool.

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