Insights Gained from Inadvertent Monitoring of Slow-Growing Melanomas Using Digital Dermoscopy

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Melanoma, much like other cancers, encompasses a wide variety of biological behaviors. For example, lentigo maligna melanoma classically grows over many years, while nodular melanoma can present as a tumor that grows rapidly within a few months. The recent addition of the E, for Evolving or change, to the ABCD mnemonic (Asymmetry, Border irregularity, Color variegation, Diameter greater than 6 mm) for early melanoma recognition has provided the public and medical community an additional tool with which to identify potential malignancy. Such change can manifest itself as an alteration in symmetry, border, color, and/or diameter, as well as elevation and other traits.

Melanomas that grow slowly, however, may undergo subtle changes that are imperceptible to the naked eye. These tumors may continue to grow without proper diagnosis and management until clinically noticeable features lead to a biopsy; at this point, the tumor may have a worse prognosis than if it had been caught earlier. Since

From the Editors

In this issue of The Melanoma Letter, Drs. Terushkin, Marghoob, and Argenziano present an excellent review of “slow-growing melanoma,” a clinical entity that their own recent research has greatly illuminated. This phenomenon takes on greater importance given the increased recognition of the lifesaving potential of melanoma screening and the growing emphasis on change as the most sensitive indication of melanoma.

Public and physician education on melanoma detection have moved beyond the ABCDs to emphasize outlier lesions. The “Ugly Duckling” sign has been popularized to connote the morphologic outlier that looks different than other spots, while the ABCDs have been modified to include “E” for “evolving” to connote the dynamic outlier, a lesion that is changing relative to other spots. Dermoscopy has increased the sensitivity for finding both morphologic and dynamic outliers, with digital dermoscopy an especially effective tool for following the dynamic outliers over time. Lesions that look clinically similar can differ under dermoscopy, and lesions that appear unchanged clinically can manifest change under dermoscopy. The challenge of slow-growing melanomas is that they can defy even dermoscopic recognition.
Slow-growing Melanomas

From page 1

decreasing mortality from an existing melanoma centers around early diagnosis and treatment, identifying relevant subtle changes in lesions that do not quite fulfill the classic ABCD features of melanoma is an area that deserves attention.

Over the last two decades, considerable efforts have been made to develop and refine non-invasive imaging techniques to examine features of skin lesions that would otherwise be clinically undetectable. Dermoscopy is by far the most widely studied of these techniques, with more than 1,800 published articles to date, as per PubMed. Recently, the benefits of dermoscopic examination as a diagnostic aid for melanoma were illuminated by the publication of a study that assessed subtle dermoscopic changes in melanoma characterized by slow growth. These findings add to our understanding of melanoma pathogenesis and could affect future management of this disease.

Dermoscopy as an Aid For Melanoma Diagnosis

In dermoscopy, a magnifying glass and a fluid interface or polarized light allow the visualization of structures within the epidermis and papillary dermis that are normally invisible to the naked eye. A vocabulary pertaining to structures, colors, organization, and patterns visualized with dermoscopy is used, much like the language used when describing skin lesions and eruptions during routine clinical examination. Particular dermoscopic structures are suggestive of melanoma; some of these include atypical network, streaks, irregular dots and globules, chrysalis-like structures, irregular blotches, and blue-white structures.

Multiple studies have provided support for using this device in the management of patients with pigmented lesions. For example, a meta-analysis of 27 studies showed that dermoscopy increases accuracy in diagnosing melanoma by 49 percent compared to the unaided eye. A more recent meta-analysis of studies specifically performed in a clinical setting reported an odds ratio of 15.6 for the accurate diagnosis of melanoma compared to the naked eye (adjusted to 9.0 with the removal of two outlier studies). One study also demonstrated a decreased number of benign lesions biopsied for each malignant lesion biopsied (the so-called benign-to-malignant ratio) following the introduction of dermoscopy into clinical practices. Another showed that the number of patients referred for biopsy was lower in the dermoscopy group (9.0 percent) compared to the non-dermoscopy group (15.6 percent) during a screening trial.

Dermoscopic Strategies

The dermoscopic diagnosis of melanoma can be made by following one of several strategies. First, clinicians may choose from many established analytical diagnostic algorithms, such as the ABCD rule (Asymmetry, Borders, Colors, Differential structural components or Dermoscopic structures) or the CASH algorithm (Colors: few vs. many, Architecture: order vs. disorder, Symmetry vs. asymmetry, Homogeneity vs. Heterogeneity), to distinguish malignant from benign pigmented lesions. With the algorithm approach, a calculation is made based on the number of melanoma-specific structures present; if a certain threshold is reached, a biopsy is recommended. The second option is based on the concept of the “ugly duckling,” whereby a lesion that stands out from the surrounding lesions, even if appearing banal itself, should raise suspicion. A third option is to use the “beauty and the beast” sign; the dermoscopic pattern of the lesion is compared to nine established, typical recurrent benign patterns, and if it strays from any of these patterns, a biopsy is suggested.

Digital Dermoscopy

The advent of digital dermoscopy has allowed clinicians to assess dermoscopic changes in lesions much like clinicians routinely follow clinical changes. This involves capturing a dermoscopic image at baseline and comparing it to an image captured during a follow-up appointment. This technique has been utilized in two situations.

First, it has been used in instances when a lesion may appear suspicious on dermoscopy but does not fulfill the diagnostic criteria in any of the algorithms or strategies described above. The approach to managing such lesions, coined “short-term mole monitoring,” was proposed by Menzies, et al, who followed equivocal lesions for a median of three months and biopsied all lesions that exhibited any morphological change, except a global change in global pigmentation or the number of milia-cysts. Overall, 11 percent of the lesions that changed were diagnosed as melanoma. These cases did not exhibit any classical dermoscopic melanoma features and might have been missed had they not been monitored.

Second, digital dermoscopic monitoring has been used in patients with multiple clinically atypical moles, who are at high risk for melanoma. The concept of long-term dermoscopic monitoring was introduced by Kittler, et al, who followed 499 lesions — 408 histologically confirmed nevi and 91 melanomas — over the course of 8 months. The group found that a majority of melanomas did not exhibit melanoma-specific structures at baseline and started to exhibit...
them only with time. The authors created a list of criteria for significant and insignificant changes to help clinicians using this technique to decide whether or not to biopsy. The purpose of both short- and long-term mole monitoring is to decrease unnecessary biopsies while detecting as many featureless melanomas as possible.

As the evidence supporting the use of dermoscopy in clinical practice has grown, so has instruction in and use of the technique. According to a survey of US dermatology residency programs conducted in 2000, approximately 51 percent of respondents used dermoscopy. A follow-up survey of new residents conducted in 2009 found that usage had soared to 84 percent. This increased use in residency programs will likely translate to greater use in clinical practice by graduates.

The Existence of Slow-growing Melanoma

The development of digital dermoscopic monitoring has provided a remarkable opportunity to study subtle changes in melanoma and gain insights on its behavior and pathogenesis. In 2010, Argenziano and colleagues was as significant as their overall conclusion, since it provided an opportunity for additional investigations. In fact, our group (Terushkin V, Dusza SW, Scope A, et al) used this rich database to take a closer look at longitudinal changes in select dermoscopic features with the aim of obtaining insights into melanoma progression. Specifically, we compared baseline to follow-up dermoscopic images and assessed changes in global dermoscopic pattern, organization, colors and structures, as well as how these changes related to lesion size.

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excised from patients in 15 pigmented lesion clinics across the US, Europe, and Australia, who were followed with digital dermoscopy. Melanomas that were followed for at least 12 months prior to excision were selected from a database of over 10,000 melanomas. The biopsy delays for these patients had been either unintentional or, in rare circumstances, due to patient refusal. The study set ultimately consisted of 103 melanomas with baseline and follow-up dermoscopic images. After a median follow-up of 20 months, most lesions were still in situ or at the early invasive stage, with only three lesions showing tumor thickness of 1 mm or more. The most frequent baseline characteristics were asymmetrical pigmentation, reticulate overall pattern, and regression features. Most melanomas showed minor to moderate changes over time, and major changes were visible only after a mean follow-up of 33 months.

Longitudinal Changes

The creation of the image data set by Argenziano and colleagues was as significant as their overall conclusion, since it provided an opportunity for additional investigations. In fact, our group (Terushkin V, Dusza SW, Scope A, et al) used this rich database to take a closer look at longitudinal changes in select dermoscopic features with the aim of obtaining insights into melanoma progression. Specifically, we compared baseline to follow-up dermoscopic images and assessed changes in global dermoscopic pattern, organization, colors and structures, as well as how these changes related to lesion size.
Our study set included 92 of the 103 lesions originally compiled by Argenziano and colleagues;14 11 melanomas were excluded because they had inadequate resolution for detailed dermoscopic analysis of their structures. At baseline, the most common global dermoscopic patterns included homogeneous (40 percent), reticular-homogeneous (31 percent), and reticular (16 percent) patterns. On follow-up, reticular and reticular-homogeneous lesions tended to develop more homogeneous areas. Lesions also tended to become more disorganized (baseline=63 percent versus follow-up=79 percent). Comparing changes in colors, we found that on follow-up, the color light brown decreased while dark brown color increased in prominence. We also found that the colors red, white, gray, blue, and black, respectively, increased in frequency on follow-up compared to baseline (baseline: 29 percent, 3 percent, 18 percent, 6 percent, and 33 percent versus follow-up: 41 percent, 10 percent, 31 percent, 13 percent, 45 percent).

The most common dermoscopic structure encountered at baseline was a pigment network, exhibited by 56 lesions (60.9 percent); the network was atypical in a third of these cases. On follow-up, we observed a trend toward disappearance of the pigment network and a concomitant increase in structureless areas. Melanoma-specific structures such as negative network, blue-white structures, and blotches also appeared on follow-up imaging. Figures 1 and 2 exemplify dermoscopic changes observed in two cases in the data set.

Finally, we explored the relationship of change in lesion size with changes in the total number of structures and colors. Of the 92 lesions, 15 showed no change in size, and 55 increased by ≤ 2 mm, while 22 grew by > 2 mm. Those lesions with the greatest change in size were more likely to exhibit changes in structures and colors ($\chi^2 = 14.3$, $p = 0.027$).

What Dermoscopic Changes Tell Us about Progression

Our current understanding of melanoma progression is limited. Imaging technologies such as dermoscopy and confocal microscopy, combined with histopathological examination of tumors, can help expand our knowledge. In 2009, Scope, et al16 proposed a progression model of superficial spreading melanoma (SSM). According to this model, the first step involves proliferation of neoplastic melanocytes along an undulating dermal-epidermal junction (DEJ). In the second step, remodeling of the DEJ and superficial dermis occurs. The DEJ is flattened with an associated increase in vascularity, fibroplasia, and inflammation.

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This creates an ideal environment for invasion of neoplastic melanocytes into the dermis, which is the third step in the melanoma progression model. Notably, several of our findings support this model. That is, we observed that the pigment network, which histologically correlates with a proliferation of melanocytes along the DEJ, became less prominent or more blurred on follow-up, coinciding with an increase in tan structureless areas.

Continued on page 5
The development of these structureless areas was shown by Anessi, et al\textsuperscript{17} to correlate with proliferation of melanocytes along a flattened DEJ. We also found that blue-white structures, which are thought to correlate histopathologically with fibroplasias and melanophages in the superficial dermis, became more prominent or newly developed on follow-up. Finally, we found an increase in frequency of the color red on follow-up, which according to Scope’s model\textsuperscript{16} may reflect increased lesion vascularity.

**Future Directions and Clinical Implications**

Utilizing digital dermoscopic monitoring, we learned not only of the existence of slow-growing melanoma, but also that it is possible to detect subtle changes in these lesions that may have been missed with the naked eye. When caring for patients with pigmented lesions, it is important to pay particularly close attention to subtle changes such as the blurring of the pigment network, increasing disorganization, the appearance of melanoma-specific structures, and development of new colors as potential markers of this subtype of melanoma. It is also important to be aware that these lesions show minimal changes in overall size. These studies underscore the value of non-invasive digital imaging technology as a diagnostic aid for melanoma, as well as an opportunity for furthering our understanding of melanoma biology.

**References**