Identification of Clinically Featureless Incipient Melanoma Using Sequential Dermoscopy Imaging

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Objectives: To examine the role of sequential dermoscopy imaging in detecting incipient melanoma and to elucidate the impact of length of follow-up on the relevance of observed changes.

Design: Baseline and follow-up images of melanomas and melanocytic nevi excised only because of changes across time were inspected on a computer screen and assessed according to prospectively defined criteria. Lesions were stratified into 3 groups according to the length of follow-up.

Setting: Three hospital-based referral centers in Europe and Australia.

Patients: Four hundred sixty-one patients selected for digital dermoscopy monitoring.

Main Outcome Measures: Description and comparison of dermoscopy features and changes in melanomas and melanocytic nevi at baseline and after follow-up.

Results: We inspected baseline and follow-up images of 499 melanocytic skin lesions from 461 patients. The histopathologic diagnosis was melanoma in 91 cases and melanocytic nevus in 408. Most melanomas (58.2%; n=53) were in situ, and the median thickness of invasive melanomas was 0.38 mm. Dermoscopy features of melanomas and nevi did not differ significantly at baseline. After follow-up of 1.5 to 4.5 months, 61.8% of the melanomas showed no specific dermoscopy features for melanoma. This value declined to 45.0% after follow-up of 4.5 to 8.0 months and to 35.1% after more than 8.0 months. We could not differentiate melanomas and changing nevi by means of observed changes or dermoscopy features when follow-up was shorter than 4.5 months. With longer follow-up, melanomas tended to enlarge asymmetrically with architectural and color changes, and nevi tended to enlarge symmetrically without architectural and color changes.

Conclusions: Sequential dermoscopy imaging detects incipient melanomas when they are still featureless. Interpretation of changes observed during follow-up depends on the length of follow-up.

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Early recognition of cutaneous melanoma is of utmost importance to improve the prognosis of this potentially fatal disease. Primary melanoma of the skin usually begins in the epidermis with the proliferation of single cells as melanoma in situ. If melanoma is diagnosed at this noninvasive stage, the patient will be cured by excision of the primary tumor, but if melanoma becomes invasive, the chance of cure decreases as invasion thickness increases.

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Recognition of early melanoma is a challenge to every dermatologist. Inspection of the skin using the unaided eye may be accurate for the diagnosis of advanced cases, but it is inaccurate for the diagnosis of incipient melanoma. Dermatologists are using noninvasive diagnostic tools such as dermoscopy to improve the detection rate of early melanoma, but even dermoscopy has limitations. Melanomas and, in particular, incipient melanomas may lack dermoscopy features specific to this disease. It has recently been shown that these “featureless” melanomas can be recognized by sequential dermoscopy imaging. Stolz et al and Braun et al were the first to report on the use of sequential digital dermoscopy for the surveillance of melanocytic skin lesions. This technique is used for short-term monitoring of single melanocytic lesions that are not suggestive enough to warrant excision at the patient’s first visit but not completely inconspicuous. In this setting, the criteria for selecting a lesion for monitoring have been clearly defined by...
Menzies et al., and the follow-up time is restricted to 3 months. Another reason to use sequential imaging may be to monitor patients with multiple melanocytic nevi. In this setting, the physician usually monitors multiple lesions. The criteria for selecting lesions in patients with multiple nevi have not yet been clearly defined. Follow-up is usually longer than 3 months and varies from 6 to 12 months (long-term monitoring).

Different criteria have been proposed by Kittler et al (long-term monitoring) and Menzies et al (short-term monitoring) to discriminate between relevant and irrelevant changes. In contrast to short-term monitoring, in which any change leads to a decision to excise, long-term monitoring has a series of “significant” changes requiring excision compared with “nonsignificant” changes found in benign nevi. A limitation is that the criteria for both approaches have been established on series of cases that included fewer than 10 melanomas. The aim of this study was to evaluate differences between changes observed in melanomas and melanocytic nevi in a large series of cases and to elucidate the impact of length of follow-up on the relevance of observed changes.

Sequential dermoscopy images of melanocytic lesions included in this study were collected from 3 different institutions: (1) the Department of Dermatology, University of Vienna Medical School; (2) the Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital; and (3) the EMCO Clinic in Bad Dürnb erg. All 3 centers offer a specialized unit equipped with digital imaging systems for the examination of pigmented skin lesions. The institutions in Austria are equipped with the MoleMax II system (Derma Instruments, Vienna), and the Sydney Melanoma Diagnostic Centre is equipped with SolarScan (Polartechnics Ltd, Sydney). The former system offers a maximum field of view of 1 cm with magnification ×30, the latter a field of view of 2.4×1.8 cm with magnification ×12.5. Both systems store images in an uncompressed digital image format: Windows bitmap with a resolution of 800×600 (Molemax II) or tagged image format with a resolution of 760×570 (SolarScan).

Criteria for the selection of lesions for short-term monitoring by the Sydney Melanoma Diagnostic Centre have been described previously. In general, except for some lesions suggestive of lentigo maligna of the face, lesions selected for short-term monitoring were either (1) symmetrical or, more frequently, near symmetrical in pigmentation pattern and had a patient history of change or (2) were more asymmetrical, with greater architectural disorder without specific dermoscopy features of melanoma without a history of change. All the lesions were flat or only superficially raised.

Patients selected for long-term monitoring by the institutions in Austria had multiple nevi. At the patient’s first visit, suggestive lesions were excised to rule out melanoma. The threshold for excision varied depending on the number and the morphologic appearance of lesions, the patient’s history regarding melanoma, and the patient’s preferences. The remaining melanocytic lesions, including completely inconspicuous lesions, were referred for digital monitoring.

The cases included in this study were consecutive cases from the 3 participating institutions. All the lesions were excised because of changes across time identified during follow-up by means of digital dermoscopy. Low-quality digital images and images of lesions exceeding the maximum field of view of the imaging system either at baseline or at follow-up were excluded. All excised lesions were subjected to standard histopathologic analysis. The cases from Austria were independently reviewed by 2 expert dermatopathologists. Only 2 cases were withdrawn because of discordant histopathologic diagnosis.

**PRESENTATION OF IMAGES AND DEFINITION OF CRITERIA**

The dermoscopy images of melanoma and melanocytic nevi were presented on a computer screen to 2 experts in dermoscopy (H.K., L.T., S.M., and P.G.) in Austria and Australia blinded to the histopathologic diagnosis. Initially, baseline images and follow-up images were presented separately. Each image was evaluated according to the dermoscopy criteria defined by Menzies et al based on pattern analysis as published elsewhere. This method was chosen because it has consistently been shown to have higher sensitivity for the diagnosis of melanoma compared with other dermoscopy methods and naked eye examination. In short, these criteria include 2 negative features of melanoma (symmetry of pattern and a single color) and 8 positive features (regression [scarlike depigmentation or multiple blue-gray dots], blue-white veil, multiple brown dots, radial streaming, pseudopods, peripheral black dots and globules, broadened network, and multiple colors). Although not included in the original study by Menzies et al., the presence of an atypical vasculature was also scored as a positive feature of melanoma. Atypical vasculature is defined as a mixture of polymorphous linear vessels (not comma vessels), dotted vessels, and hairpin or red globular vessels.

Baseline and follow-up images were then presented side by side on the computer screen to evaluate changes across time. We defined and scored the following criteria for change. Change in the number of brown globules, (5) the appearance of pseudopods, and (6) the appearance of radial streaming (streaks arranged radially at the periphery). Color changes were defined as changes in color or pigmentation and included (1) lighter or darker (brown) pigmentation of the whole lesion, (2) lighter or darker (brown) pigmentation of parts of the lesion, (3) the appearance of a new color (possible colors: brown, red, blue, and black), (4) loss of a preexisting color, (5) an increase or decrease in the erythema reaction, and (6) pure depigmentation (loss of any color and replacement by white).

**STATISTICAL ANALYSIS**

Continuous data are given as mean±SD unless otherwise specified. Mann-Whitney and t tests were used to compare continuous data and χ² and exact tests were used to compare proportions. Logistic regression was used for multivariate analysis of the association of type of change and histopathologic diagnosis. The multivariate logistic model was age adjusted and included only variables that reached statistical significance in the
RESULTS

GENERAL DATA

The study sample consisted of baseline and follow-up images of 499 melanocytic skin lesions excised because of changes across time. The lesions were from 461 patients (mean±SD age, 44±17 years; 55% women). Most lesions were located on the back (n=243; 48.7%). Follow-up was 1.5 to 4.5 months for 236 lesions (47.3%), 4.5 to 8.0 months for 81 lesions (16.2%), and longer than 8.0 months for 182 lesions (36.5%). The histopathologic diagnosis was melanoma in 91 cases and melanocytic nevus in 408 cases. Patients whose changing lesion was a melanoma were significantly older (mean±SD age, 52±15 years) than those whose changing lesion was a melanocytic nevus (mean±SD age, 42±16 years; P<.001). Of the 91 melanomas, 53 (58.2%) were in situ. The median Breslow thickness of invasive melanomas (n=38) was 0.38 mm (range, 0.20-0.90 mm). The proportion of in situ melanomas was 77.8% (n=21) among melanomas excised after 1.5 to 4.5 months of follow-up, 45.0% (n=9) among melanomas excised after 4.5 to 8.0 months, and 62.2% (n=23) among melanomas excised after more than 8.0 months of follow-up (P=.20).

DERMOSCOPY CHARACTERISTICS OF BASELINE IMAGES

The dermoscopy features of baseline images of melanoma and melanocytic nevi are given in Table 1 and Table 2. The distribution of dermoscopy features did not differ significantly between melanoma and nevi except for broadened network, which was more frequently found in melanomas (7.7%) than in nevi (1.2%; P=.002). At baseline, 61.5% of the melanomas did not show any positive features of melanoma compared with 68.4% of nevi (P=.43). The frequency of negative features of melanoma was higher in lesions selected for long- vs short-term monitoring, indicating greater architectural disorder in short-term monitored lesions. In particular, symmetry of structure was found in 30.9% of lesions with follow-up longer than 4.5 months compared with only 8.5% of lesions with follow-up shorter than 4.5 months (P<.001). A single color was found in 21.3% of lesions with follow-up longer than 4.5 months compared with only 3.0% of lesions with follow-up shorter than 4.5 months (P<.001).

DERMOSCOPY CHARACTERISTICS OF FOLLOW-UP IMAGES

The dermoscopy features of follow-up images are given in Table 2. The proportion of melanomas without any positive dermoscopy features for melanoma decreased from 61.8% after follow-up of 1.5 to 4.5 months to 45.0% after follow-up of 4.5 to 8.0 months to 35.1% after follow-up of longer than 8.0 months (P<.001). When follow-up was longer than 8.0 months, the proportion of lesions with positive features of melanoma was significantly higher among melanomas than among nevi, but we did not find significant differences between follow-up images of nevi and melanoma when follow-up was shorter than 8.0 months (Table 2).

CHANGES OBSERVED DURING FOLLOW-UP

Baseline and follow-up images were scored for enlargement, architectural changes, and color changes. The longer the follow-up interval, the higher the proportion of enlarging lesions. In lesions with 1.5 to 4.5 months of follow-up, only 36.9% of lesions enlarged compared with 75.6%...
in the group with follow-up between 4.5 and 8.0 months and 82.4% in the group with follow-up of longer than 8.0 months (P<.001). The frequencies of all types of changes by histopathologic diagnosis and length of follow-up are given in Table 3. In lesions with follow-up ranging from 1.5 to 4.5 months, we found no relevant differences between nevi and melanoma regarding single changes that they can be detected when they are noninvasive. Even when melanomas are detected later in the course of the disease, when the criteria for melanoma become more obvious, the chances are still good that they can be detected when they are noninvasive.

In the present study, we collected 499 melanocytic skin lesions from 3 different centers in Europe and Australia. All the lesions were selected to be monitored by means of digital dermoscopy and were finally excised because of changes across time. Histopathologically, 91 lesions were diagnosed as melanomas and 408 as melanocytic nevi. Most melanomas detected by follow-up were in situ melanomas.

It has always been a matter of debate whether these melanomas could have been spotted at the patient’s first visit. However, by comparing baseline images of melanomas and nevi using prospectively defined criteria, we showed that melanomas selected for sequential imaging could not be differentiated from melanocytic nevi at baseline. At baseline, most melanomas did not show even a single specific dermoscopy criterion. Hence, dermoscopy criteria for detecting melanoma do not allow the identification of incipient melanomas. It seems that most melanomas grow slowly and mainly horizontally at the beginning. Even when melanomas are detected later in the course of the disease, when the criteria for melanoma become more obvious, the chances are still good that they can be detected when they are noninvasive.
This raises the question of how quick melanoma progresses from a clinically inconspicuous, small lesion that cannot be differentiated from a melanocytic nevus to a clear-cut melanoma. To address this important issue, we reexamined only the follow-up images without comparison with the baseline images. After follow-up of 1.5 to 4.5 months (short-term follow-up), 61.8% of the melanomas showed no positive dermoscopy-specific features of melanoma. It is likely that these melanomas would have been left untouched without the information regarding change. Although some melanomas developed specific features, such as pseudopods, broadened pigment network, and black dots beyond 4.5 months, the overall frequency of melanomas without a positive feature was still high (45.0% when follow-up was 4.5-8.0 months and 35.1% when follow-up was >8.0 months).

In summary, we found that the frequency of melanoma-specific criteria increased with the length of follow-up, but, most importantly, we found that incipient melanomas may remain featureless for a certain period. We believe that except for detection by chance, without follow-up information these melanomas would remain unrecognized until they develop specific dermoscopy criteria. The information regarding change helps detect melanoma during this inconspicuous period.

A major motivation for this study was to address the question of whether all types of changes are relevant and which types differentiate melanomas from changing melanocytic nevi. Not unexpectedly, the answer is that it depends on the length of follow-up. For short-term monitored lesions, we could not detect a single type of change or a combination of changes that reliably differentiated melanomas and changing nevi. This confirms the recommendation by Menzies et al.9 that every lesion showing any change after 1.5 to 4.5 months should be excised. The situation is different when follow-up is longer than 4.5 months. After this period, melanomas tend to show an asymmetrical increase in size and architectural changes. Melanocytic nevi, on the other hand, tend to enlarge symmetrically, without architectural changes. This confirms the recommendation by Kittler et al.6 to divide changes across time into significant and nonsignificant changes. Color changes in melanoma (in particular the appearance of new colors) become more evident after 8.0 months of follow-up (Table 3). This may indicate that color variegation, usually said to be an important diagnostic clue for melanoma, is a feature of melanomas that have existed for a long time. Surprisingly, architectural changes were found more frequently in short-term monitored lesions. One explanation might be that differences in the resolution of the images provided by the imaging systems used in Australia and Austria are responsible for this finding. Another possible explanation is the difference between lesions selected for short- and long-term follow-up. There was a relatively high frequency of completely inconspicuous lesions with symmetry of pattern or only a single color among long-term monitored lesions compared with short-term monitored lesions. It is possible that this difference at baseline affected the frequency of architectural changes at follow-up.

The proportion of in situ melanomas was highest after short-term follow-up (77.0% of all melanomas in this group). It declined to 45.8% after follow-up of 4.5 to 8.0 months and increased again to 62.2% when follow-up was longer than 8.0 months. There is no straightforward explanation for this finding, but it may also be attributed to differences in selecting lesions for short- and long-term monitoring. The criteria for selecting lesions for short-term monitoring have been defined by Menzies et al. Short-term monitoring has been tailored to single lesions that do not show criteria for melanoma but that are not completely inconspicuous. Digital monitoring for longer periods has been used mainly for patients with multiple nevi. However, criteria for the selection of lesions in patients with multiple nevi have not been clearly defined. In the Department of Dermatology in Vienna, where most of the lesions with longer follow-up have been collected for this study, the policy is to monitor as many lesions as possible, including completely inconspicuous lesions. This creates a considerable workload, and the question of whether this policy is cost-effective remains unresolved. The high frequency of in situ melanomas and the low invasion thickness of invasive melanomas in this sample suggest that this procedure may actually save lives by diagnosing melanoma as early as possible when the probability of metastatic disease is either zero (for in situ melanomas) or exceedingly low (for early invasive melanomas).

Two approaches to digital monitoring are examined in this study. Short-term monitoring occurs in the setting of a suggestive lesion without dermoscopy features of melanoma. This is usually found in nevi symmetrical or, more frequently, near symmetrical in pigmentation pattern and having a patient history of change or in more asymmetrical lesions but without specific dermoscopy features of melanoma and without a history of change. All the lesions are flat or only superficially raised. Short-term monitoring can, therefore, be found in any patient irrespective of their phenotype. The median suggested follow-up for short-term monitoring is 3 months. Data were collected in a range up to 4.5 months, allowing for variations in patient appointment times. In contrast, long-term monitoring usually occurs in patients with multiple nevi or other high-risk phenotypes for developing primary melanoma. Melanocytic lesions, including completely inconspicuous nevi, are referred for digital monitoring at standard surveillance periods. Hence, for a median of 6 months of follow-up (chosen because it represents the shortest surveillance period for very high-risk patients), a range of 4.5 to 8.0 months allowed variation in appointment times. Data were also collected at yearly follow-up (within a range >8.0 months). The current recommended short-term follow-up is 3 months, and long-term follow-up is 6 to 12 months depending on overall patient risk factors for developing a new primary melanoma.

In summary, digital dermoscopy monitoring detects melanoma earlier than any other noninvasive procedure when specific criteria for melanoma are still absent. It is a safe procedure if the criteria for selecting lesions for monitoring are applied consistently. The major clues for detecting incipient melanomas are subtle morphologic changes. The interpretation of these changes depends on the length of follow-up. When combining the
findings of this study and works previously described, our suggested guidelines for the management of melanocytic lesions after digital monitoring are as follows. When a lesion is unchanged after short- or long-term monitoring, it can be considered benign. Further imaging may occur depending on physician discretion, such as at the next standard patient surveillance interval. Except for a change in the number of milia-like cysts, or an overall increase or decrease in pigmentation without architectural change due to sun exposure in the perimonitoring period, any morphologic change after short-term monitoring leads to excision of the lesion (Figure 1). For long-term monitoring, some nonsignificant changes occur commonly in nevi. These are a darker and lighter overall appearance, changes in the number or distribution of brown globules, decrease in the num-

Figure 1. Melanoma in situ identified by short-term (3-month) monitoring. A, Baseline image of inconspicuous lesion without dermoscopic features of melanomas. B, The follow-up lesion image shows an asymmetrical increase in size (arrow), with scattered areas of architectural change. C, The histopathologic study shows melanocytes arranged in irregular nests and as single cells, some of them disposed in higher layers of the epidermis (hematoxylin-eosin, original magnification ×40). Histopathologic diagnosis: melanoma in situ.

Figure 2. Melanoma in situ identified by long-term (16-month) follow-up in a patient with multiple melanocytic nevi. A, The baseline image. B, The follow-up image shows an asymmetrical increase in size and the appearance of a pigment network at the periphery. C, The histopathologic study shows melanocytes arranged in irregular nests and as single cells, some of them disposed in higher layers of the epidermis (hematoxylin-eosin, original magnification ×40). Histopathologic diagnosis: melanoma in situ.
umber of black dots, disappearance of an inflammatory reaction, or disappearance of parts of the pigment network and replacement by diffuse brown pigmentation. Such changes do not require an excision biopsy. Apart from these nonsignificant changes, a certain proportion of monitored nevi will show symmetrical enlargement during follow-up without structural changes. This proportion is higher in younger individuals. Usually more than 1 melanocytic nevus in a patient will show symmetrical enlargement, and excision is not required. When asymmetrical enlargement, focal changes in pigmentation and structure, regression features, or change in color (appearance of new colors) occur during long-term follow-up, a decision to excise must be considered to rule out melanoma even in an otherwise inconspicuous melanocytic lesion (Figure 2).

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