Frequency and Characteristics of Enlarging Common Melanocytic Nevi

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Objective: To analyze the frequency and characteristics of enlarging common melanocytic nevi.

Design: Cohort study using digital epiluminescence microscopy (ELM) for documentation and follow-up, with a median follow-up interval of 11.4 months.

Setting: A dermatology department at a university hospital in Vienna, Austria.

Patients: One thousand six hundred twelve melanocytic nevi appearing clinically as common nevi, obtained from 385 patients (mean [±SD] age, 34.2 ± 14.8 y; 55.6% female).

Interventions: Follow-up examination and documentation by digital ELM.

Main Outcome Measures: Frequency of enlarging nevi according to age and comparison of ELM features observed in enlarging and nonenlarging nevi.

Results: Enlargement was found in 5.3% (n = 86) of nevi. The frequency of enlarging nevi was inversely related to age (P < .001), in that enlarging nevi were common in patients younger than 20 years and relatively rare in older age groups. Epiluminescence microscopy revealed a peripheral rim of brown globules in 48.8% (n = 42) of enlarging nevi. In contrast, a peripheral rim of brown globules was found in only 0.7% (n = 11) of nevi without enlargement (P < .001). Enlarging nevi that were excised in children and adolescents showed no histological signs of atypia. In older age groups, 48.1% of excised enlarging nevi that were clinically diagnosed as common nevi showed some histological signs of atypia. None of the excised enlarging lesions was histologically diagnosed as melanoma.

Conclusions: The frequency of enlarging common nevi is inversely related to age. In the absence of clinical signs of atypia, enlargement alone does not indicate malignancy. A peripheral rim of brown globules is a characteristic ELM feature of symmetrically enlarging melanocytic nevi.

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DATA ARE available in the English literature relating to the growth and natural history of congenital nevi and dysplastic nevi. Only limited data exist on the modifications observed over time in acquired common melanocytic nevi, and, to our knowledge, the frequency and characteristics of enlarging common nevi have never been assessed in an epidemiological study.

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Documentation, which is a prerequisite to study the modifications over time of common melanocytic nevi, is a time-consuming procedure when using conventional photographs. Follow-up of a large number of melanocytic nevi using photographic close-ups is impracticable, considering the time and work needed for retrieval and comparison of photographs. In contrast, digital epiluminescence microscopic (DELM) images of melanocytic skin lesions can be stored, sorted, retrieved, and compared easily, and therefore are especially useful for the follow-up of melanocytic skin lesions. Furthermore, epiluminescence microscopy (ELM) of melanocytic skin lesions reveals numerous elementary structures that are not seen with total body photographs or with photographic close-ups without ELM. Therefore, we used DELM to study the modifications observed over time in acquired common melanocytic nevi and analyzed the frequency and characteristics of enlarging acquired common nevi.
METHODS

Melanocytic skin lesions appearing clinically as common nevi were examined using DELM and were electronically stored using a DELM imaging system (MoleMax II; Derma Instruments, Vienna, Austria). Digital images were acquired under standardized conditions, including illumination, gain, and color calibration of the recording unit, and were stored without compression in bitmap format. The pixel resolution of each image was 640 x 480 at 24-bit color depth.

All melanocytic skin lesions were examined by at least 2 experienced investigators (H.K., H.P., or M.B. with the unaided eye and with DELM. The clinical diagnosis of melanocytic skin lesions based on the appearance of the lesion when viewed with the unaided eye (eg, size; macular, papular, or nodular appearance; pigmentation; and configuration) and on ELM criteria as described previously.8,10,11 Nevi with clinical signs (asymmetry and variegated color) or ELM signs (irregular and/or prominent pigment network, irregular overall pigmentation, irregularly distributed black dots, whitish veil, scarlike depigmentation, and radial streaming) of atypia8,10,11 at the time of the first examination were not included in the analysis. Nevi with a maximum diameter of more than 1 cm were also excluded. Patients were recruited between November 1, 1996, and November 30, 1997. Follow-up of all patients was scheduled every 6 months (median total follow-up time, 11.4 months). Corresponding DELM images were compared at each follow-up visit. Digital ELM images of the same lesion were compared by viewing the 2 corresponding DELM images side by side on a computer screen. Enlargement of a lesion was defined as any discernible increase in the size of the lesion as determined by visual inspection of the corresponding DELM images. In addition, objective measurements were performed using digital image analysis. After automated segmentation of the lesions from the background, the area of the lesions was measured to objectively quantify an increase in size. Automated segmentation was performed using global and dynamic thresholding, and 3-dimensional clustering after transformation of the red-green-blue (RGB) image to the CIE (Commission International de l’Eclariange) colorspace, which uses a set of color standards based on mathematical modeling of human vision and light. The results of the automated segmentation were supervised by a single observer (M.S.), and were reliable and reproducible in 93.1% of all images. The remaining lesions were segmented interactively by a single observer (M.S.).

Excision of enlarging nevi was recommended in adults. Fourteen (35.0%) adult patients refused surgery and decided to continue follow-up. One patient had the excision done at another institution, and the histopathologic report and specimen could not be obtained. In children and adolescents, enlarging lesions were excised only at the patient’s or parent’s request. In total, 46 (46.5%) enlarging lesions were excised at the time of the last visit. All excised lesions were referred for standard histopathologic examination. All lesions were step-sectioned. All excised nevi were examined for histological signs of atypia, including cellular atypia, fibroplasia, elongation and bridging of rete ridges, presence of suprabasal melanocytes, and junctional nest disarray.

EVALUATION OF THE DISTRIBUTION OF BROWN GLOBULES

If brown globules were present, the distribution of brown globules within a nevus was categorized as follows: (1) scattered distribution, (2) mainly central distribution, and (3) presence of a peripheral rim of brown globules. The type of distribution of brown globules was evaluated by at least 2 ELM experts (H.K., H.P., or M.B.) without inspection of the follow-up image.

STATISTICAL ANALYSIS

Data are given as mean ± SD, unless otherwise specified. The Mann-Whitney test or the t test was performed for the comparison of continuous data, and the χ² test was used for the comparison of proportions. Relative risks and their 95% confidence intervals were calculated according to standard procedures. All given P values are 2-tailed, and P<.05 was considered statistically significant.

RESULTS

GENERAL CHARACTERISTICS

Follow-up images of 1612 acquired common melanocytic nevi were obtained from 385 patients (mean age, 34.2 ± 14.8 years; 55.6% female). The median number of nevi with follow-up was 3 per patient (range, 1-23). The median total follow-up interval was 11.4 months (range, 3.2-21.4 months). The clinical diagnosis included 381 junctional nevi (23.6%), 1114 compound nevi (69.1%), and 117 dermal nevi (7.3%). The mean area of the nevi was 0.31 cm² (95% confidence interval, 0.30-0.32 cm²).

FREQUENCY OF ENLARGING NEVI

No change in size was found in 1526 (94.7%) of the nevi. Only 86 nevi (5.3%) exhibited an enlargement during follow-up. We observed an age-related linear decline in the frequency of enlarging nevi (for trend, P<.001; Table 1). Enlargement of nevi was observed frequently in patients younger than 20 years and was relatively rare in older age groups (Table 1). Symmetric enlargement was found in 72 enlarging lesions (83.7%). Only 14 enlarging nevi were examined for histological signs of atypia, including cellular atypia, fibroplasia, elongation and bridging of rete ridges, presence of suprabasal melanocytes, and junctional nest disarray.

Table 1. Frequency of Enlarging Nevi by Age Group

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>No Enlargement</th>
<th>Enlargement</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>10 (41.7)</td>
<td>14 (58.3)</td>
<td>24</td>
</tr>
<tr>
<td>11-20</td>
<td>136 (87.7)</td>
<td>19 (12.3)</td>
<td>155</td>
</tr>
<tr>
<td>21-30</td>
<td>484 (94.5)</td>
<td>28 (5.5)</td>
<td>512</td>
</tr>
<tr>
<td>31-40</td>
<td>444 (96.1)</td>
<td>18 (3.9)</td>
<td>462</td>
</tr>
<tr>
<td>41-50</td>
<td>245 (98.8)</td>
<td>3 (1.2)</td>
<td>248</td>
</tr>
<tr>
<td>&gt;50</td>
<td>207 (98.1)</td>
<td>4 (1.9)</td>
<td>211</td>
</tr>
<tr>
<td>Total No.</td>
<td>1526 (94.7)</td>
<td>86 (5.3)</td>
<td>1612</td>
</tr>
</tbody>
</table>

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ing nevi (16.3%) showed focal enlargement with an additional change in shape. The size increased by a median factor of 1.3-fold (range, 1.04- to 2.6-fold). Enlargement was found in 3 of 117 dermal nevi (2.6%), 60 of 1114 compound nevi (5.4%), and 23 of 381 junctional nevi (6.0%) (P = .34). Enlargement of nevi was somewhat more frequent in the head and neck area than at other body sites, but this difference was not statistically significant (P = .21).

CHARACTERISTICS OF ENLARGING NEVI

A peripheral rim of brown globules was a characteristic ELM feature of enlarging nevi (Figure 1). This peripheral rim of brown globules was present in 42 (48.8%) 86 enlarging nevi. In contrast, it was found in only 11 nevi without enlargement (0.7%) (P < .001). The relative risk of enlargement was 28-fold higher (95% confidence interval, 20- to 39-fold higher) for nevi with a peripheral rim of brown globules compared with nevi without a peripheral rim of brown globules. Table 2 shows the frequency of enlarging nevi according to the type of distribution of brown globules. At the time of the first documentation, enlarging nevi were generally smaller than nonenlarging nevi (0.22 ± 0.16 cm² vs 0.31 ± 0.18 cm²; P < .001).

Surgical excision followed by histopathologic examination was performed in 40 enlarging nevi (46.5%). Thirteen excised enlarging nevi of children and adolescents (patients younger than 20 years) showed no histological signs of atypia and were diagnosed histologically as common nevi. In patients 20 years and older, 13 (48.1%) of 27 excised enlarging nevi that were clinically diagnosed as common nevi showed some histological signs of atypia: fibroplasia and elongation and bridging of rete ridges. Since other signs of atypia characteristic for an atypical (Clark, dysplastic) nevus were not found, these lesions were therefore not diagnosed as atypical nevi.

None of the excised enlarging lesions was histologically diagnosed as melanoma.

Histological examination also disclosed that relatively heavily pigmented junctional nests of nevus cells...
in the periphery of the lesion are probably the histopathologic correlate of the peripheral rim of brown globules seen with ELM (Figure 2).

MORPHOLOGIC CHANGES OTHER THAN ENLARGEMENT

Morphologic changes other than enlargement were identified in 503 lesions (31.2%). A total of 131 nevi (8.1%) showed an increase in the overall pigmentation and appeared darker. In 191 lesions (11.8%) a decrease in the overall pigmentation (lighter appearance) was observed. An inflammatory reaction that was not present at the initial presentation was observed in 53 (3.3%) of the follow-up images. An increase in the number of brown globules was observed in 105 lesions (6.5%), and 42 lesions (2.6%) showed a decrease in the number of brown globules. In 17 nevi (1.1%), the pigment network became more prominent over time. This was always correlated with an increase in the overall pigmentation (darker appearance) of the lesion. In 31 lesions (1.9%), a pigment network that was not visible in the initial image could be identified in the follow-up image. In 18 lesions (1.1%), a part of the pigment network disappeared over time and was replaced by a diffuse light brown pigmentation. Black dots appeared in 16 follow-up images (1.0%). Peripheral depigmentation (halo phenomenon) or partial disappearance was found in 8 lesions (0.5%).

Table 2. Frequency of Enlarging Nevi by Epiluminescence Microscopic (ELM) Appearance

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>No Enlargement</th>
<th>Enlargement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown globules absent (n = 636)</td>
<td>628 (98.7)</td>
<td>8 (1.3)</td>
</tr>
<tr>
<td>Brown globules present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scattered distribution (n = 835)</td>
<td>800 (95.8)</td>
<td>35 (4.2)</td>
</tr>
<tr>
<td>Central distribution (n = 88)</td>
<td>87 (98.9)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Peripheral rim (n = 53)</td>
<td>11 (20.8)</td>
<td>42 (79.3)</td>
</tr>
<tr>
<td>Total (N = 1612)</td>
<td>1526 (94.7)</td>
<td>86 (5.3)</td>
</tr>
</tbody>
</table>

Our study also demonstrates that enlarging nevi in patients 20 years and older are infrequent but not rare. Our data suggest that enlarging common nevi in older age groups deserve more attention than in children or adolescents. In adults, a considerable proportion of enlarging nevi that were clinically diagnosed as common nevi showed some histological signs of atypia but not the full complement of histopathologic criteria required for a lesion to be designated as atypical (Clark) nevus. Also, none of the excised enlarging nevi was found histologically to be a melanoma. This finding has to be interpreted with caution, but it demonstrates that enlargement alone is a weak indicator for impending or incipient malignancy even in adults. However, enlargement of melanocytic skin lesions may be a valuable additional criterion to differentiate clinically atypical nevi from early melanomas. Follow-up studies of patients with multiple atypical nevi using the technique of DELM are needed to investigate the diagnostic value of morphologic change in clinically atypical nevi.

We also showed that the presence of a peripheral rim of brown globules is characteristic for enlarging nevi. Nearly 80% of nevi with a preexisting peripheral rim of brown globules showed enlargement during follow-up. Histopathologic examination showed that large nevus cell nests in the epidermal-dermal junction zone are probably the histopathologic correlate of the peripheral rim which supports previous hypotheses.\(^{16,17}\) Formation of junctional nevus cell nests in the periphery and appearance of a peripheral rim of brown globules may represent a specific feature of symmetrically and rapidly enlarging benign melanocytic skin lesions. The presence of a peripheral rim of brown globules in pigmented Spitz nevi has been previously described by Steiner et al.,\(^{18}\) where it was interpreted to be pathognomonic. Our present finding clearly shows that this view has to be corrected. Since Spitz nevi are usually enlarging lesions when excised, the peripheral rim of brown globules should now be considered a sign of nevus growth and not a pathognomonic feature of Spitz nevi.

Morphologic changes other than enlargement were found in 31.2% of acquired common nevi. As reported...
by Stanganelli and coworkers, some of these modifications may be related to sun exposure. The frequency of modifications observed in our study are comparable to a smaller follow-up study by Stolz and coworkers. Braun et al observed modifications over time in 69% of nevi. This high frequency of modifications may be explained by the fact that this study included a high proportion of Spitz nevi. Braun and coworkers also did not report the patients’ ages, so their results cannot be compared directly with ours.

Follow-up of melanocytic skin lesions using DELM allows time-saving comparison of actual and previous images of melanocytic skin lesions. Using this technique, we demonstrated that rapidly enlarging common nevi have specific ELM features. We also demonstrated that enlargement alone does not indicate impending or incipient malignancy. Since our study was restricted to acquired common melanocytic nevi, the diagnostic value of DELM for the follow-up of atypical nevi has to be assessed further.

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