In Vivo Confocal Scanning Laser Microscopy of a Series of Congenital Melanocytic Nevi Suggestive of Having Developed Malignant Melanoma

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Objective: To determine the utility of confocal scanning laser microscopy (CSLM) in the in vivo evaluation of congenital melanocytic nevi (CMNs) that are suggestive of having developed melanoma.

Design: The CMNs suggestive of melanoma by clinical and dermoscopic examination were imaged by CSLM, and the findings correlated with the features seen on dermoscopic and histologic examination.

Setting: Dermatology clinic specializing in pigmented lesions.

Patients: Seven patients with clinically irregular small to medium CMNs.

Interventions: The areas imaged by CSLM were sampled with 3-mm punch biopsy specimens. The entire lesion was subsequently excised. The punch biopsy specimens were step sectioned horizontally to correlate with the CSLM images. Excised samples were step sectioned and processed routinely. Histologic features observed on CSLM were correlated with the features seen on dermoscopic and light microscopic examination.

Main Outcome Measure: Correlation of the structures seen using CSLM with the dermoscopic and histologic features of CMNs and melanoma.

Results: The CSLM illustrated histologic characteristics of CMNs, including the presence of hyperpigmented keratinocytes, nevus cells, melanophages, and a normal “honeycomb” epidermal architecture. Features suggestive of melanoma were not evident by CSLM in 6 histologically proven benign CMNs. Histologic features associated with melanoma, such as an increased number of intraepidermal atypical melanocytes (pagetoid) and loss of normal epidermal cellular architecture, were identified by CSLM in 1 lesion, which on histologic analysis revealed melanoma in association with a CMN.

Conclusion: Our results illustrate that CSLM may be useful for clinicopathologic correlations and for the preliminary noninvasive diagnosis of pigmented neoplasms in vivo.

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Approximately 1% of infants are born with at least 1 congenital melanocytic nevus (CMN). Melanoma may develop in association with some CMNs, and the magnitude of the risk of developing melanoma within CMNs appears to correlate with the size of the nevus, with the highest risk attributed to the largest nevi.1,2 Despite the fact that small (<1.5-mm) to medium (1.5 to 10.0-cm)3 nevi are reported to be at relatively low risk of developing an associated melanoma, the management of these CMNs remains controversial. Some physicians cite the reports that have documented an increased risk of melanoma developing in such nevi and recommend prophylactic excision of many of these CMNs.4,5 On the other hand, many physicians regard the risk of melanoma developing in small to medium CMNs to be low and the complete excision of large CMNs to be impractical. They therefore recommend clinical observation with biopsy or surgical excision of CMNs that are clinically atypical or develop suspicious changes noted during follow-up examinations.6,4

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As patients grow, their CMNs may develop and undergo subtle changes in size, color, and texture. Many patients with these changing CMNs undergo biopsy to rule out the possible development of melanoma. Most of these lesional biopsy specimens show the hist-
Confocal imaging was first performed over the entire lesion. The area deemed to be suggestive of malignant transformation under clinical and dermoscopic examination was then imaged in depth by CSLM. A commercially available near-infrared CSLM (Vivascope 1000; Lucid Inc, Henrietta, NY) was used. This instrument uses a diode laser at 830 nm with an operating maximal power of 35 mW. It images with a spatial resolution of 0.5 to 1.0 µm in the lateral dimension and 4 to 5 µm in the axial dimension. Skin sites under investigation were immobilized to less than 25 µm by using a tissue ring and template fixture that provided mechanical contact of the skin with the CSLM. The ×30 objective lens of numerical aperture 0.9 was applied to the skin, between which either water (refractive index, 1.33) or gel (refractive index, 1.34) was placed. This liquid interface served as the immersion medium. Images were displayed at 14 frames per second on a computer monitor. Captured images were obtained using Vivavscope 1000 software. Notably, confocal images depicted in this article are static and 2-dimensional, which is markedly different from the dynamic and 3-dimensional images observed using CSLM when performed live. Confocal scanning laser microscopy provides the operator with immediate visualization of the skin in both the horizontal and vertical plane, thereby allowing the observer to appreciate the overall architecture of the area being scanned and allowing the operator to hone in on areas of interest.

HISTOPATHOLOGIC ANALYSIS

A 3-mm punch biopsy specimen was obtained from the area imaged in depth by CSLM. The tissue specimen was sectioned horizontally to correlate with images of CSLM. The remainder of the lesion was excised and step sectioned in the traditional vertical fashion. The excised tissue was fixed in formalin and embedded in paraffin. After routine processing, the slides were stained with hematoxylin-cosin.

CLINICAL AND DERMOSCOPIC FINDINGS

Figures 1, 2, 3, 4, 5, 6, and 7 exemplify the clinical and dermoscopic features of the 7 melanocytic lesions presented. Patient 1, a 74-year-old white woman (Figure 1A), had a CMN that measured 1.4 cm in greatest diameter on her right arm. As per her history, the nevus had been present since birth and had become uniformly darker during the past 3 years. This lesion was symmetric, round, and light and dark brown and had hypertrichosis. Dermoscopic examination (Figure 1B) revealed asymmetry and sharp borders. The colors included light brown, dark brown, blue-gray, and black. The structures included a disrupted pigmented network, peripherally placed black dots, and streaks. The TDS was calculated to be 6.9 and the modified TDS was 8.1, indicating that this lesion was highly suggestive of melanoma.

Patient 2, an 83-year-old white woman, had a 1.6-cm black melanocytic lesion on the left side of her chest. As per her history, the nevus had been present since birth and had become uniformly darker in color and flatter during the past 3 years. The CMN (Figure 2A) had irregular borders and a raised mamillated surface. Dermoscopic examination (Figure 2B) revealed asymmetry and sharp borders. The colors included light brown, dark

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brown, blue-gray, and black. The structures included a disrupted pigmented network, peripherally placed black dots, and streaks. The pen mark at the superior periphery was used as a guide for the punch biopsy.

Patient 3, a 49-year-old white man, had a 3.0-cm lesion on his chest that was fairly symmetric, oval, and brown in color and was studded with 3 violaceous papules (Figure 3A). The patient reported that the nevus has been present since birth and had recently developed the 3 dark papules within it. Dermoscopic examination (Figure 3B) revealed asymmetry and sharp borders. The colors included light brown, dark brown, and blue-gray. The structures included globules and structureless areas.

Patient 4, a 28-year-old white woman, had a 1.3-cm melanocytic lesion on her left flank with sharp borders, color variegation, hypertrichosis, and a mammillated surface (Figure 4A). She reported that this lesion had been present since birth and had recently increased in size, (REPRINTED) ARCH DERMATOL/VOL 141, NOV 2005 WWW.ARCHDERMATOL.COM
changed in contour, and bled on one occasion. At the edge of the nevus was a focus of new pigment spillage. Dermoscopic examination (Figure 4B) revealed asymmetry and sharp borders. The colors included light brown, black, and blue-gray. The structures included a pigmented network, black dots, streaks, and structureless areas. The TDS was 6.4 and the modified TDS was 7.6, both indicative of melanoma.

Patient 5, a 47-year-old white woman, presented with a 1.2-cm irregular melanocytic lesion on her left breast. She denied any change in the nevus, which had been present since birth. The nevus was asymmetric and had irregular borders and multiple colors (Figure 5A). Dermoscopic examination (Figure 5B) revealed asymmetry and sharp borders. The colors included light brown, dark brown, black, and blue-gray. The structures included a pigmented network, black dots, streaks, and structureless areas. The TDS was calculated to be 7.4 and the modified TDS was 6.6, again both suggestive of melanoma.

Patient 6, a 16-year-old white girl, revealed a 1.2-cm irregular hypertrichotic melanocytic lesion on her right arm, which was reported to have been present since birth. The nevus had an oval shape with a uniform brown color except for a peripheral edge that had a 2-mm dark brown macule (Figure 6A). Dermoscopic examination (Figure 6B) revealed prominent reticulation and some streaks. Dermoscopic examination of the entire lesion revealed asymmetry and sharp borders. Colors included light brown and dark brown. The structures included a pigmented network, globules, and black dots.

Patient 7, a 70-year-old white man, presented with a 1.4-cm melanocytic lesion on the left side of his chest (Figure 7A). This lesion was noted at birth, and its presence was documented on a photograph taken when the patient was 2 years old. He reported that the lesion had recently increased in size and changed in contour, with the development of a darkly pigmented area on the medial aspect of the nevus. Dermoscopic examination (Figure 7B) revealed asymmetry and sharp borders. Colors included light brown, dark brown, and black. The structures included a pigmented network, globules, and black dots.
nation of the lateral aspect of the lesion revealed cobblestone-like globules (Figure 7B). Examination of the entire lesion revealed asymmetry and sharp borders. Dermoscopic findings of the hyperpigmented medial aspect of the nevus are illustrated in Figure 7B. Colors included light brown, dark brown, blue-gray, and black. The structures included a pigmented network, globules, and black dots. The TDS was 6.9 and the modified TDS was 8.1, both highly suggestive of melanoma.

CONFOCAL AND HISTOLOGIC FINDINGS

Figure 8A exemplifies an image by CSLM of the dermoepidermal junction of the CMN of patient 1. Confocal scanning laser microscopy showed hyperpigmented keratinocytes at the dermoepidermal junction. Keratinocytes were characterized by a bright image signal of cohesive cells with variably bright cytoplasm that formed rings around papillae. The papillary dermis appeared dark. There was no evidence of an increased number of single melanocytes or a nested melanocytic proliferation throughout all levels of the epidermis or superficial dermis. Figure 8B illustrates the corresponding histologic features of a compound melanocytic nevus in the traditional vertical orientation. Rare nests were present at the dermoepidermal junction; however, most of the melanocytes were located in the reticular dermis. Histologic analysis revealed few if any melanocytes in the papillary dermis, corresponding with the dark papillary dermis seen with CSLM.

Figure 9A illustrates an image by CSLM for patient 2. Again, CSLM showed hyperpigmented keratinocytes at the dermoepidermal junction, which were characterized by a bright image signal of cohesive cells with variably bright cytoplasm that formed rings around papillae. Confocal scanning laser microscopy also revealed focal clusters of melanophages within the papillary dermis. Melanophages were characterized as plump, bright cells with ill-defined cytoplasmic borders. There was no evidence of an atypical melanocytic proliferation throughout all levels of the epidermis or superficial dermis. Corresponding histologic sections showed symmetric and heavily pigmented intradermal melanocytic proliferation with a benign CMN pattern. No intraepidermal or junctional atypical melanocytic proliferations were seen. No nests or single melanocytes were present in the papillary dermis. Instead, clusters of melanophages were seen around papillary dermal capillaries, as illustrated by the horizontal section in Figure 9B.28

For patients 3 and 4 (Figure 10A and Figure 11A), CSLM illustrated nests of nevus cells within the papillary dermis represented by monomorphous, bright white, round structures in clusters. The cellular outlines between individual nevus cells within nests were difficult to distinguish. The bright image signals of the individual cells within nests fused to form a spherical structure of variable size. Imaging with CSLM of all levels of the epidermis failed to reveal an atypical melanocytic proliferation. Corresponding histologic analysis (Figure 10B...
and 11B) demonstrated nests of nevus cells at the dermoeipidermal junction and within the papillary dermis consistent with those seen using CSLM. Again, no evidence of an atypical melanocytic proliferation within the epidermis or superficial dermis was observed on conventional histologic analysis, and complete histologic examination revealed a benign melanocytic nevus with a CMN pattern.

For patient 5 (Figure 12A), CSLM illustrated hyperpigmented keratinocytes along the dermoeipidermal junction. In addition, evidence of round, monomorphous, sharply demarcated, brightly imaged, single cells were identified within the superficial dermis. Given the architectural context and morphologic features of these cells compared with corresponding histologic features (Figure 12B), these cells were most consistent with single nevomelanocytes. Imaging with CSLM of all levels of the epidermis failed to reveal any atypical melanocytic proliferation (ie, there were no irregular-shaped, large, polymorphic, heterogeneously bright reflectance melanocytes, and there were no irregular dendrites or melanocytes in the spinous layer), and complete histologic examination revealed a benign melanocytic nevus with a CMN pattern.

Figure 13A exemplifies an image by CSLM from patient 6 at the level of the dermoeipidermal junction. Again, epidermal keratinocytes were visualized at the basal cell layer, characterized by the presence of bright white cytoplasmic granules within monomorphous cohesive cells with variably bright cytoplasm that formed rings around papillae. The papillary dermis appeared dark, corresponding to the relative paucity of melanin-containing cells within the imaged area of the superficial dermis. There was no evidence of an increased number of single melanocytes or an atypical nested melanocytic proliferation at all levels of the epidermis with CSLM, which is confirmed by representative histologic analysis (Figure 13B).

Figure 14A illustrates an optical section by CSLM taken from the lightly pigmented lateral aspect of the nevus of patient 7 at the level of the papillary dermis. Nevomelanocytes can be identified by their bright, round, monomorphous distribution within the papillary dermis. Individual cells appeared homogeneously white and were clustered in nests within the dermal papillae. Confocal scanning laser microscopy failed to identify any features suggestive of melanoma (Figure 14A). Figure 14B illustrates the representative histologic features, showing nests of nevomelanocytes at the papillary dermis. Figure 15A illustrates an optical section from the darkly pigmented medial aspect of this nevus. This section was taken at the deep spinous layer of the epidermis and illustrates a number of distinct cellular features. First, the regular honeycomb pattern characteristic of a normal spinous layer with CSLM is not present. Individual keratinocytes and keratinocyte cell borders are difficult to detect, and bright refractile particles of variable size were seen throughout the epidermis. Furthermore, an increased number of solitary melanocytes with dendrites were recognized in the mid and
**Figure 10.** Confocal scanning laser microscopy image of patient 3. A, A nest of nevomelanocytes within the papillary dermis in the lesion is seen (arrow). B, Histologic features (horizontal section) corresponding to the confocal image demonstrate the nevus nests (arrow, hematoxylin-eosin; original magnification ×200).

**Figure 11.** Confocal scanning laser microscopy image of patient 4. A, A nest of nevomelanocytes within the papillary dermis (arrow). B, Histologic features (horizontal section) corresponding to the confocal image demonstrate the nevus nests (arrow, hematoxylin-eosin; original magnification ×200).
Figure 12. Confocal scanning laser microscopy (CSLM) image of pigmented epidermal keratinocytes along the dermoepidermal junction (arrowheads) in the lesion of patient 5. A, Single cells representing nevomelanocytes at the papillary dermis (arrows). B, Corresponding histologic features in a conventional vertical section of a nevus with congenital features demonstrate epidermal keratinocytes along the dermoepidermal junction and nevomelanocytes at the papillary dermis. The horizontal line indicates the level of the corresponding CSLM image (hematoxylin-eosin; original magnification ×40).

Figure 13. Confocal scanning laser microscopy image at the dermoepidermal junction of patient 6. A, Epidermal keratinocytes (arrowheads) are visualized at the basal layer. B, Histologic features (horizontal section) corresponding to the confocal image demonstrate epidermal keratinocytes (arrowheads) at the basal layer and no evidence of an increased number of melanocytes at the dermoepidermal junction or papillary dermis (hematoxylin-eosin; original magnification ×200).
upper epidermis, which suggested in situ melanoma. Figure 15B shows a corresponding histologic section of the intraepidermal component of superficial spreading melanoma. As evidenced by CSLM, individual cells are seen at varying levels of the epidermis. Examination of the entire nevus by conventional histologic analysis confirmed the presence of in situ melanoma arising within a CMN.

The Table provides a synopsis of the CSLM, histologic, and dermoscopic correlates.

### COMMENT

Although some researchers believe that the risk of melanoma developing in small and medium CMNs is low, others have reported an increased risk of malignancy in such nevi. Thus, the opinions regarding medical management vary widely. Some physicians recommend lifelong observation of small and medium CMNs that clinically are not atypical and do not undergo any suspicious changes. These patients are routinely followed up by a physician and are encouraged to examine the nevus themselves on a monthly basis. Biopsy or excision is performed only if changes occur that are suggestive of melanoma. To aid in the follow-up examinations, many physicians find baseline photographs of the CMN to be helpful.35 On the other hand, some physicians recommend prophylactic excision of the CMN to prevent melanoma and possibly improve cosmesis.

We present 7 cases of CMN in which most patients reported a history of change. The clinical and dermoscopic features of all 7 CMNs were suggestive of melanoma. However, it is well known that CMNs can have features in common with melanoma on both clinical and dermoscopic examination,36 thus making the in vivo differentiation between CMN and melanoma difficult. For this reason, we evaluated these 7 cases by CSLM. In vivo CSLM demonstrated some of the cellular characteristics of histologically proven benign CMNs and melanoma that arose within a CMN. These features were subsequently confirmed by histologic examination of the excised lesions. This study was not intended to give an exhaustive description of the cellular constituents of pigmented lesions by CSLM, as has previously been reported,28,29 but rather to demonstrate the clinical applicability of CSLM as an aid in ruling out melanoma.

Confocal scanning laser microscopy works by tightly focusing a low-power, near-infrared laser beam on a specific point in the skin and detecting only the light reflected from the focal point through a pinhole-size spatial filter. This beam is then scanned horizontally over a 2-dimensional grid to obtain a horizontal microscopic section. Adjustments can be made in the focal length of the beam, allowing the microscope to image a series of horizontal planes stacked vertically, with an axial thickness of 2 to 5 µm. The imaging depth in normal skin is limited to 300 to 400 µm sec-
primary to limited penetration of the near-infrared light through the skin. This allows for visualization of the epidermis, dermoepidermal junction, and papillary dermis with near-histologic resolution. Previously, CSLM has been explored for its use on melanocytic lesions. Melanin and melanosomes provide strong cytoplasmic contrast for the light source and therefore consistently appear bright on confocal microscopy, allowing for visualization of pigmented cells. Langley et al evaluated 40 melanocytic neoplasms by CSLM and proposed criteria to distinguish nevi from melanoma. However, the specificity or sensitivity of their criteria has not been tested yet, and it seems premature to apply them for diagnosis. In our

**Figure 15.** Confocal scanning laser microscopy (CSLM) image of the darkly pigmented medial aspect of the nevus in patient 7 at the level of the deep spinous layer. A, Pagetoid spread of atypical melanocytes is visualized in a chaotic growth pattern. Note the predominance of atypical single cells over nests and the dendritic processes of the large melanoma cells (arrowheads). B, Corresponding vertical histologic section illustrates malignant melanoma in situ, superficial spreading pattern, with pagetoid spread of melanocytes (arrowheads). The horizontal line illustrates the level of the corresponding CSLM image (hematoxylin-eosin; original magnification ×200).

**Table.** Correlates Between Findings of Confocal Scanning Laser Microscopy, Histopathologic Findings, and Dermoscopy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Confocal Features</th>
<th>Equivalent Histologic Correlates (Features)</th>
<th>Equivalent Dermoscopic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bright white cytoplasmic granular structures at the level of the dermoepidermal junction</td>
<td>Basal hyperpigmented keratinocytes</td>
<td>Pigmented network</td>
</tr>
<tr>
<td>2</td>
<td>Bright white cytoplasmic granular structures at the level of the dermoepidermal junction; confluence of bright white within the papillary dermis</td>
<td>Basal hyperpigmented keratinocytes; melanophages within the papillary dermis</td>
<td>Pigmented networks; blue-gray area (“peppering”)</td>
</tr>
<tr>
<td>3</td>
<td>Clusters of round bright white (hypogenic) structures in the papillary dermis</td>
<td>Nevus cell nests in the papillary dermis</td>
<td>Brown globules</td>
</tr>
<tr>
<td>4</td>
<td>Clusters of round bright white (hypogenic) structures in the papillary dermis</td>
<td>Nevus cell nests in the papillary dermis</td>
<td>Brown globules</td>
</tr>
<tr>
<td>5</td>
<td>Bright white cytoplasmic granular structures at the level of the dermoepidermal junction; single round bright white structures within the papillary dermis</td>
<td>Basal hyperpigmented keratinocytes; nevomelanocytes at the papillary dermis</td>
<td>Pigmented network; no dermoscopic correlates established (may correspond to brown dots)</td>
</tr>
<tr>
<td>6</td>
<td>Bright white cytoplasmic granular structures at the level of the dermoepidermal junction</td>
<td>Basal hyperpigmented keratinocytes</td>
<td>Pigmented network</td>
</tr>
<tr>
<td>7</td>
<td>Clusters of round bright white (hypogenic) structures in the papillary dermis; bright white pleomorphic single cells within the deep spinous layer of the epidermis</td>
<td>Nevus cell nests in the papillary dermis; pagetoid spread of atypical melanocytes within the epidermis</td>
<td>Cobblestone-like globules; multiple dots</td>
</tr>
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</table>
own experience, pagetoid intraepidermal spread detectable by CSLM seems to be one of the most reliable findings suggestive of intraepidermal melanoma. The strength of this parameter comes from the fact that it represents an important, albeit not entirely specific, feature for the diagnosis of melanoma by conventional histologic analysis.

In this study, CSLM was able to demonstrate important histologic features of 7 CMNs that were suggestive of melanoma by history, clinical examination, and dermoscopic examination. In patients 1 through 6, CSLM revealed a normal epidermal and dermoepidermal architecture and did not identify an increased number of atypical or dendritic melanocytes, abnormal single cells (pagetoid), or an irregularly nested melanocytic proliferation at the dermoepidermal junction, thus helping to rule out the diagnosis of melanoma developing within the epidermis or at the dermoepidermal junction. The uniform configuration of the basal cell layer as evidenced by CSLM made the probability of melanoma low and dermal invasion unlikely. This is in sharp contrast to the CSLM images described in patient 7, where the loss of normal cytologic architecture with the presence of melanocytes within the upper epidermis helped to raise suspicion for in situ melanoma by CSLM.

The CSLM images of patient 5 illustrate an important point. Although a single-cell proliferation was evidenced within the superficial dermis, the ability to characterize the morphologic features of the cells (ie, regular shape, comparatively small cell size, and monomorphic cellular architecture) helped to classify this lesion as benign by CSLM. In all 7 lesions, correlation between the images of CSLM with the findings of routine histopathologic analysis was demonstrated. These findings illustrate the potential application of CSLM as a noninvasive screening tool in the assessment of CMNs that undergo clinical changes suggestive of melanoma.

The depth of penetration of the near-infrared light imposes a limitation on the ability of CSLM to fully assess the deep dermal cells of pigmented lesions. Confocal scanning laser microscopy failed to identify cellular structures within the reticular dermis. Dermal melanocytes with evidence of maturation as seen on routine histologic examination could not be visualized by CSLM. Like dermoscopy, the inability of CSLM to image within the deeper dermis excludes important information from the diagnostic process. However, the limitation of not being able to fully evaluate the deeper dermis of small to medium CMNs is mitigated by the recognition that most melanomas arising in these smaller CMNs appear to originate at the dermoepidermal junction. Illig et al³⁰ reported a series of 52 CMNs measuring less than 10 cm in diameter that developed melanoma within the nevus. The histologic assessment of all 52 melanocytic neoplasms revealed that the melanoma originated at the dermoepidermal junction and none had an intradermal origin.³⁰ Hence, most of the important histologic information required for treatment decisions in smaller CMNs could most likely be ascertained from imaging of the epidermis and dermoepidermal junction. Furthermore, since the depth of nevus cell infiltration in CMNs has been found to correlate with the size of the lesion,³⁷ the histologic evaluation of most large CMNs by CSLM may not be optimal with the current state of optical penetration depth.

In conclusion, this brief series illustrates that CSLM may become an additional tool for the noninvasive histologic study of pigmented lesions such as CMNs. Confocal scanning laser microscopy allows for the identification of features characteristic of nevi and melanoma. However, future studies are needed to determine the sensitivity and specificity of diagnoses rendered or suspected by CSLM. Technical improvements will probably result in better histologic detail. Although an ×30 objective lens was used in this study, higher magnification is currently available with an ×100 objective lens, allowing for increased cellular detail. In addition, as technological advances occur, CSLM will likely improve its resolution and optical penetration depth to allow for increased visualization within the dermis. Notwithstanding, the images described in this pilot study along with the dermoscopic and histologic correlations illustrate the potential application of CSLM for clinicopathologic study and for the preliminary diagnoses of pigmented neoplasms.³⁰

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