In 1975, Kornberg and Ackerman coined the term pseudomelanoma for benign, recurrent melanocytic nevi that demonstrate clinical and histologic findings suggestive of melanoma following partial surgical removal. Similarly, melanocytic nevi under the effects of external insults such as laser therapy and chronic irritation, or endogenous conditions such as lichen sclerosus, Stevens-Johnson syndrome or toxic epidermal necrolysis, and other blistering diseases, may also result in significant atypia, leading to confusion with melanoma.

CONCLUSIONS AND RELEVANCE To our knowledge, this is the first reported case of melanoma arising in EB simplex-affected skin. It highlights the difficulty in differentiating melanoma from an EB nevus. Despite the increasing awareness of EB nevi, a high index of suspicion for melanoma should be maintained, and early biopsy is recommended when evaluating large pigmented lesions in patients with EB.
and color variegation. A 4-mm punch biopsy specimen was obtained from a portion of the plaque, and a diagnosis of melanoma was rendered.

The patient was subsequently referred to our melanoma clinic for evaluation and treatment of this pigmented lesion. Examination was notable for an 11.5 × 7.5-cm red and black ulcerated plaque with irregular brown-black scalloped borders encompassing the entire left heel and extending onto the lateral aspect and the arch of the foot (Figure 1). A flat component at the periphery of the lesion comprised coalescing brown-black macules and patches. An intact bulla was also observed proximal to the ulcerated plaque. Given her history of chronic, severe EBS involving the left heel, both melanoma and EB nevus were considered. The differential diagnosis also included a melanoma arising in the background of an EB nevus.

Routine histologic evaluation demonstrated characteristic features of EBS, with prominent basilar clefting (Figure 2). In addition, a contiguous lentiginous proliferation of small melanocytes with mild to moderate cytologic atypia was noted along the dermal-epidermal junction. Unlike the reported cases of EB nevi,8,10 the rete ridges were elongated rather than effaced. Florid pagetoid spread of atypical melanocytes was also observed focally. A few distorted nests of atypical melanocytes were noted in the superficial dermis underlying the bulla. Although the possibility of an atypical EB nevus was entertained based on its occurrence on EB-affected skin and large size, the severity of the cytologic and architectural atypia strongly favored an invasive melanoma (Breslow depth of at least 1.10 mm and Clark level IV).

Several treatment options were discussed by our Multidisciplinary Melanoma Tumor Board, including (1) scouting biopsy specimens to rule out a background of EB nevus and to map out the extent of the melanoma, followed by excision of the melanoma only; (2) wide local excision of the entire pigmented region with 2-cm margins and staged reconstruction; or (3) below-the-knee amputation. After thorough discussion with the patient, the final decision was to proceed with below-the-knee amputation based on the concern for persistent disease and the high complication rate anticipated with free-flap reconstruction of a weight-bearing surface in the setting...

Figure 1. Clinical Photographs of a Large, Atypical Pigmented Lesion on the Patient’s Left Foot and Ankle

A, Lateral view shows an intact epidermolysis bullosa simplex bulla above the ankle and a few smaller vesicles within the pigmented plaque. B, Plantar view of the red and black ulcerated plaque covering the entire heel.

Figure 2. Initial 4-mm Punch Biopsy Specimen

Characteristic basilar clefting of epidermolysis bullosa simplex is present. In addition, there is a contiguous lentiginous proliferation of atypical melanocytes involving elongated rete ridges. Florid pagetoid spread is also noted toward the center of this photomicrograph (hematoxylin-eosin, original magnification ×100).

Figure 3. Amputation Specimen

Sections from the pigmented plaque show unequivocal acral lentiginous melanoma with areas of prominent epidermolysis bullosa simplex-related basilar clefting (hematoxylin-eosin, original magnification ×40). Higher magnification reveals sheets of markedly atypical melanocytes with mitotic activity (inset, hematoxylin-eosin, original magnification ×600).
of EB. She also elected to proceed with sentinel lymph node biopsy for staging. The amputation specimen confirmed an invasive acral lentiginous melanoma (Breslow depth of 5.05 mm, Clark level IV, and 6 mitoses per square millimeter, with ulceration) with areas of prominent basilar clefting consistent with concomitant EBS (Figure 3). Sampling of the irregular macular periphery revealed melanoma in situ without convincing evidence of a background EB nevus, and a biopsy would be advisable. Micrometastasis was detected in 1 of 5 sentinel lymph nodes. Subsequent completion lymphadenectomy revealed 15 negative lymph nodes.

Discussion

While an increased risk of squamous cell carcinoma has been well documented in patients with EB, melanoma is not particularly common in any form of EB; only patients with the recessive dystrophic form of EB have a slightly increased lifetime risk of melanoma.9 In contrast, EB nevi have become increasingly recognized as a more common finding, seen in up to 14% of patients with all forms of inherited EB.6-8,11 Epidermolysis bullosa nevi most commonly arise in the first 2 decades of life and typically involve sites of prior blisters.6,8,12,13 The clinical presentation of EB nevi can be highly suggestive of melanoma, including a rapid onset of large (up to 15 cm in diameter), irregular pigmented patches and plaques with frequent satellite lesions6,14 (Figure 4). Existing reports on EB nevi have emphasized the benign nature of these lesions. Spontaneous regression within 1 to 8 years has been documented in some cases,6,8 and there have been no confirmed reports of progression to melanoma.6,13-15 Given the low incidence of melanoma compared with EB nevi in patients with EB, some may favor close clinical follow-up and periodic dermoscopic evaluation rather than biopsy to exclude malignant melanoma in managing new-onset, atypical pigmented lesions in these patients.11,14

Abbreviation: EB, epidermolysis bullosa.
Table 2. Comparison of Histopathologic Features of EB Nevus and Melanoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EB Nevus</th>
<th>Melanoma</th>
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<tbody>
<tr>
<td>Architectural asymmetry</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Variability of melanocytic nests</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Elongation of rete ridges</td>
<td>-</td>
<td>+/- (Common in acral lentiginous melanoma)</td>
</tr>
<tr>
<td>Effacement of rete ridges</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Increased number of singly dispersed junctional melanocytes</td>
<td>+/- (Should not be confluent)</td>
<td>++ (Often confluent)</td>
</tr>
<tr>
<td>Pagetoid scatter</td>
<td>+/- (Focal if present)</td>
<td>++ (May be florid and extensive)</td>
</tr>
<tr>
<td>Dermal fibrosis</td>
<td>+/- (Lamellar scar from repeated trauma)</td>
<td>+/- (Regression)</td>
</tr>
</tbody>
</table>

Abbreviations: EB, epidermolysis bullosa; +++, usually present; +, often present; +/-, may or may not be present; - , usually absent.

Progressing spontaneously, her lesion progressed into an ulcerated plaque over the course of a year. Atypical presentations such as this should prompt a biopsy to exclude melanoma. Although some authors have found dermoscopy to be reliable in distinguishing benign EB nevi from melanoma, EB nevi possess many dermoscopic features that overlap with those of melanoma, including a multicomponent pattern, an atypical pigment network, milky red globules, and irregular dots. Unless one routinely evaluates EB nevi in a clinical practice, biopsies are likely required to definitively exclude melanoma in these difficult cases.

In addition, our case also illustrates a potential diagnostic pitfall from the histopathologic perspective. Various processes that result in damage to the skin—including blistering conditions—may lead to histopathologic changes analogous to recurrent nevi, which overlap considerably with those of melanoma. These pseudomelanomatous features include architectural asymmetry, variability of melanocytic nests, increased number of melanocytes above the dermal-epidermal junction, inflammation, and dermal scarring with splaying of melanocytes. When one is considering a histopathologic differential diagnosis of EB nevus vs melanoma arising in EB-affected skin, close attention must be given to not only the mere presence but also the degree of these atypical features (Table 2). In our patient, both florid pagetoid scattering of individual melanocytes and confluent lentiginous growth were seen, even in the initial punch biopsy specimen. While pagetoid scattering is also frequently observed in recurrent nevi and has been described in some cases of EB nevi, this change should not be florid or result in a “buckshot” pattern as seen in our case. Another distinguishing feature noted in this biopsy specimen was the contiguous lentiginous proliferation of melanocytes involving the elongated and pointy rete ridges, a characteristic finding in acral lentiginous melanoma. In contrast, EB nevi and recurrent nevi tend to demonstrate effaced or normal rete ridges, including those occurring on acral skin.

On the basis of these findings, we favored a diagnosis of melanoma despite the partial nature of the initial biopsy. We present this case to reflect the diagnostic difficulties and to compare our findings with those already described in EB nevi, in the hope of avoiding misdiagnosis or delayed diagnosis of melanoma in patients with EB. To our knowledge, this is the first reported case of melanoma arising in EBS-affected skin. Unlike EB nevi, our case demonstrated an older age of onset, progression rather than regression with time, a plaque component, elongation of rete ridges, and florid pagetoid spread. Despite the increasing awareness of EB nevi, a high index of suspicion for melanoma should be maintained in patients with atypical presentations of presumed EB nevi (older age of onset, progressive growth, and ulceration), and early biopsy should be considered in such cases.

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