Case Report/Case Series

Malignant Melanoma Arising in the Setting of Epidermolysis Bullosa Simplex
An Important Distinction From Epidermolysis Bullosa Nevus

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IMPORTANCE Patients with epidermolysis bullosa (EB) do not carry a significantly increased risk of melanoma but are prone to developing large, markedly atypical melanocytic nevi (EB nevi), which may mimic melanoma clinically and histologically. Many authors now favor a conservative approach in managing atypical pigmented lesions in patients with EB.

OBSERVATIONS We present the case of a 30-year-old woman with severe EB simplex who sought care for a large red and black ulcerated plaque. The clinical differential diagnosis included EB nevus and melanoma. An incisional punch biopsy specimen revealed an atypical melanocytic proliferation with focal florid pagetoid spread and involving elongated rete ridges, consistent with invasive acral lentiginous melanoma. The subsequent amputation was confirmatory. Micrometastasis was detected in 1 of 5 sentinel lymph nodes.

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.

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Editorial

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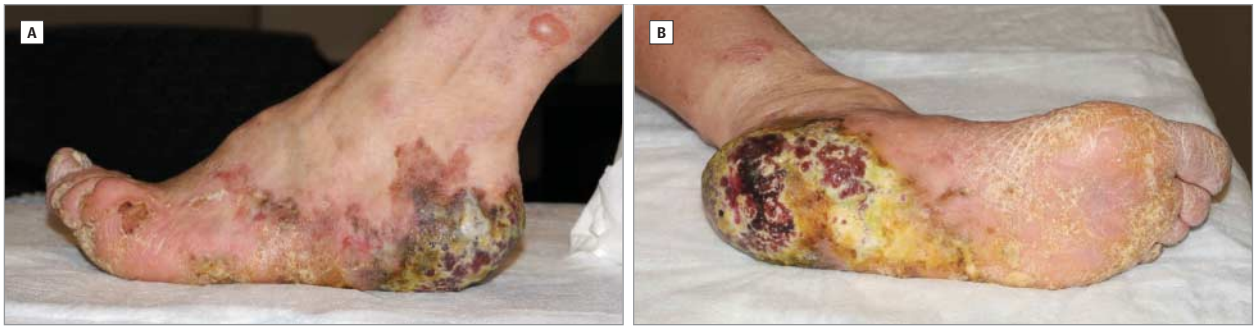
In 1975, Kornberg and Ackerman[1] coined the term *pseudomelanoma* for benign, recurrent melanocytic nevi that demonstrate clinical and histologic findings suggestive of melanoma following partial surgical removal. Similarly, melanocytic nevi under the effects of external insults such as laser therapy[2] and chronic irritation,[3] or endogenous conditions such as lichen sclerosus,[4] Stevens-Johnson syndrome or toxic epidermal necrolysis,[5] and other blistering diseases, may also result in significant atypia, leading to confusion with melanoma.

Approximately 14% of patients with various forms of epidermolysis bullosa (EB) have been described as acquiring large, eruptive, asymmetrical, clinically worrisome nevi that share similar histologic features with recurrent nevi and, at times, with melanoma. These atypical lesions were termed *EB nevi* by Bauer et al.[6] Epidermolysis bullosa nevi typically arise within sites of previous EB-related bullae and erosions. Many reports of EB nevi in children have described the lesions as rapid-growing, large, asymmetric, and irregular patches and plaques with evidence of regression and scar formation, all of which may raise suspicion for melanoma.[6-8] Despite their concerning clinical and histopathologic features, EB nevi are considered benign, with no documented reports of malignant transformation. In fact, these lesions have been described to occasionally self-involute.[6,8] Whereas the lifetime risk of melanoma is slightly increased in patients with the recessive dystrophic form of EB, EB simplex (EBS) has not been associated with an increased rate of melanoma.[9]

Report of a Case

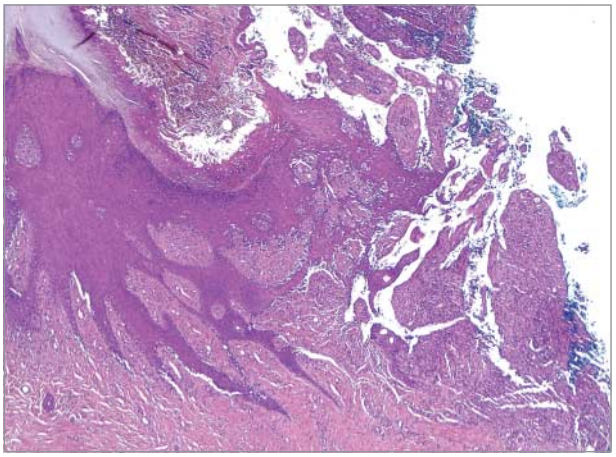
We report a case of a 30-year-old woman with a lifelong history of EBS, Dowling-Meara type, who initially sought care from her dermatologist for debilitating blistering and hyperkeratosis of the palms, soles, and extensor upper and lower extremities. Her left foot had the most severe blistering, with multiple flaccid bullae and erosions that limited her ability to walk. An EB specialist was consulted to assist in her treatment, and appropriate wound care recommendations were made. No pigmented lesions were noted at that time. Five years later, the patient sought treatment from her podiatrist for a new black discoloration underlying a callus on her left heel. The callus and the area of discoloration were debrided, resulting in a nonhealing wound. During the next 12 months, the nonhealing erosion persisted while the underlying pigmented area increased in size and developed an increasingly irregular border and color variegation. A 4-mm punch biopsy specimen was ob-

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



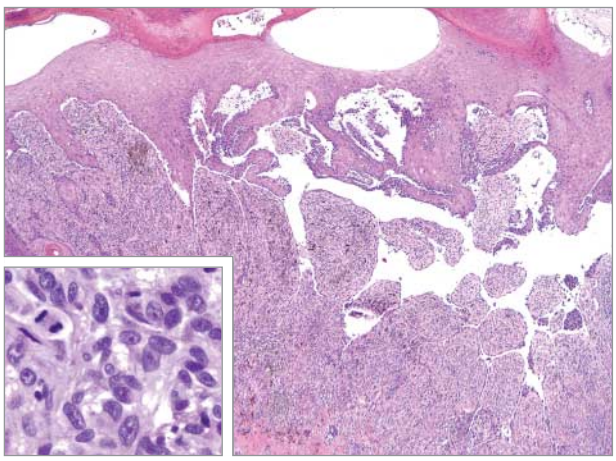
A, Lateral view shows an intact epidermolysis bullosa simplex bulla above the ankle and a few smaller vesicles within the pigmented plaque. B, Plantar view of the red and black ulcerated plaque covering the entire heel.

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).

Table 1. Comparison of the Clinical Features of EB Nevus and Melanoma

Characteristic	EB Nevus	Melanoma
Typical age group	Children and adolescents	Adults
Size	Variable; may be large	Variable; may be large
Location	Sites of prior blister	Any anatomic location
Clinical appearance	Irregular pigmented patch or plaque	Irregular papule or nodule, patch or plaque
Satellite lesions	Typical	Uncommon
Ulceration	Uncommon (blister related)	Common
Spontaneous involution	May occur 1 to 8 y after onset	No
Dermoscopy	Often has features overlapping with melanoma	Features of melanoma

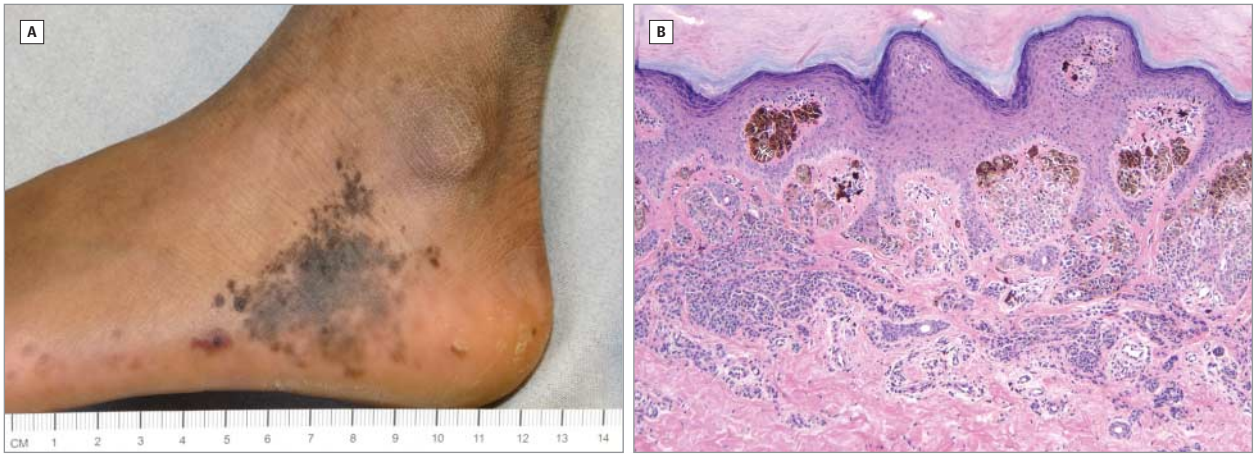
Abbreviation: EB, epidermolysis bullosa.

tained 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

Figure 4. Example of a Classic Epidermolysis Bullosa (EB) Nevus in a 9-Year-Old Girl With EB Simplex



A, Lateral view shows a large, irregular, darkly pigmented patch with multiple satellite lesions. Since the clinical and dermoscopic features of EB nevi overlap significantly with melanoma, a biopsy is often required. A similar-appearing lesion occurring in a patient without EB would be highly suggestive of melanoma, and a biopsy would be advisable. B, Punch biopsy of this EB nevus lacks any features highly suggestive of melanoma, thereby supporting the clinical impression of EB nevus (hematoxylin-eosin, original magnification ×100). Reproduced with permission from Tor A. Shwayder, MD, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.

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 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. 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 lesions[6,14] (**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]

Our patient had a decades-long history of EBS with persistent blisters and erosions involving the sole of her left heel, as well as a large, irregular pigmented plaque in the same area. Normally, such a lesion would be considered pathognomonic for melanoma in patients without EB. However, since EB nevi are much more common than melanoma in patients with EB, and because tumor ulceration may be erroneously attributed to the underlying blistering condition, a potential pitfall would be to misdiagnose the lesion in our patient as an EB nevus with a nonhealing bulla.

This case offers a few clinical clues to the diagnosis of melanoma as opposed to EB nevus (**Table 1**). Most reported EB nevi have occurred in children.[10,12,13] Spontaneous regression, sometimes resulting in a shagreen-like patch, has also been described in some cases of EB nevi.[6,8] In contrast, our patient was an adult when the lesion was first noted, and instead of regressing 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,[7,11] 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.[2-4] 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.[6] 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,[1,6,10,12] 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.[8,10,15] On the basis of these findings, we favored a diagnosis of melanoma despite the partial nature of the initial biopsy.

Table 2. Comparison of Histopathologic Features of EB Nevus and Melanoma

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

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

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 EB-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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