Epidermolysis Bullosa Nevus
An Exception to the Clinical and Dermoscopic Criteria for Melanoma
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Background: Large acquired melanocytic nevi that occur in patients with epidermolysis bullosa (EB), referred to as EB nevi, may pose a diagnostic challenge because of their clinical and dermoscopic resemblance to melanoma. These unconventional melanocytic nevi have been encountered in all categories of hereditary EB, most of them in childhood. Although some of the reported cases have an alarming clinical appearance that is indistinguishable from melanoma, long-term follow-up has confirmed the benign nature of these rarely encountered melanocytic lesions. The histopathologic patterns of these nevi range from a banal congenital pattern to the problematic persistent pseudomelanoma pattern.

Observation: We describe the clinical, dermoscopic, and histopathologic features of a large EB nevus in a toddler. Clinically, the lesion was markedly asymmetrical and irregularly pigmented with loci of stippled pigmentation and scarring, which easily fulfilled the ABCD criteria for melanoma. Accordingly, a false-positive score resulted when dermoscopy was performed. Histopathologically, a pattern of persistent melanocytic neoplasm was observed. In the following 18 months, dynamic changes of the lesion included near-complete disappearance of the pigment, which was replaced by scar, milia, and areas of healing ulcers.

Conclusion: Epidermolysis bullosa nevi are dynamic melanocytic lesions that may simulate melanoma.

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Recently, Bauer et al. proposed the term epidermolysis bullosa (EB) nevi for large acquired melanocytic nevi that are encountered in all forms of hereditary EB. Their clinical importance lies in the fact that they may simulate melanoma clinically and dermoscopically. In that 20-year prospective study of patients with EB nevi, however, no melanoma arose in association with these melanocytic nevi. We herein describe the clinical, dermoscopic, and histopathologic features of a large EB nevus in a toddler. After 18 months of follow-up, the pigment almost completely disappeared, with replacement by scar, milia, and areas of healing ulcers.

REPORT OF A CASE

A 3-year-old Korean boy with a known mutation for recessive dystrophic EB was noted on a routine follow-up visit to have a large pigmented lesion on the right thigh. The mother reported a rapid development of the pigmented lesion during a period of several months that coincided with repeated blistering at the site. Physical examination revealed a large (9 × 10-cm), markedly asymmetric, irregularly pigmented patch on the right lateral thigh (Figure 1). In addition, areas of scarring with stippled pigmentation and regressive changes (ie, hypopigmentation and scarring) were found within the lesion (Figure 1). Results of the examination revealed no palpable lymph nodes. Dermoscopic findings included an atypical network and irregular dots and globules with colors that ranged from blue to varying shades of brown and black (Figure 2). Examination of a shave biopsy specimen from an area with multiple colors revealed a cleft at the dermoepidermal junction consistent with the patient’s known recessive dystrophic EB and increased pigment within the epidermis and dermis (Figure 3). Within the epidermis, there was an uneven distribution of solitary melanocytes and a mild degree of scatter (ie, pagetoid spread) accompanied by the presence of melanin at all levels of the epidermis, including the...
cornified layer. Within the dermis, there were discretely nested, heavily melanized monomorphous melanocytes enveloped in fibrosis accompanied by numerous melanophages (Figure 4). No mitotic figures were observed. Immunohistochemical staining for Ki-67 showed no increase in the proliferative index. The histopathologic pattern was consistent with a persistent melanocytic neoplasm and, hence, the differential diagnosis was between a persistent melanocytic nevus and persistent melanoma. The monomorphous melanocytes, lack of any mitotic figures, normal proliferative index, and knowledge of the EB nevus phenomenon eventually led to the diagnosis of EB nevus. Because of the reported benign clinical course of these nevi, no therapeutic intervention was offered, only close clinical follow-up. To our surprise, during 18 months of follow-up, there was complete regression of epidermal pigment. What remained were areas of healing ulcers, hypopigmented scars, and a subtle hue of dermal pigmentation in some foci (Figure 5). Whether or not the melanocytic lesion actually regressed completely was not confirmed by histopathologic evaluation. At 24 months, the patient was well, and development of additional melanocytic lesions was not observed.

Although rarely encountered, EB nevi may not be so rare among patients with EB. Bauer et al reported a prevalence rate of 14% (12 of 86) among the patients in their EB registry. The lesions are usually encountered in children with all major categories of hereditary EB. The mean ages of patients in reported cases of recessive dystrophic EB and EB simplex are 7 and 11 years, respectively. No predilection for sex or site appears to exist, except that the lesions are encountered at the sites of repeated blisters. They are often eruptive in nature, ie, they appear rapidly and enlarge within a few weeks to a few
months. The reported lesions have ranged from 3 to 15 cm in diameter with an appearance that ranged from congenital melanocytic nevus to melanoma. The alarming clinical features included not only their large size but also the presence of marked asymmetry, irregular and/or stippled pigmentation, variegation in color, scarring, and foci of regression. On a morphologic basis alone, without the benefit of knowing the clinical context, the EB nevus may be indistinguishable from melanoma at times.

Although Gallardo et al observed no melanoma-associated dermoscopic features in their series of EB nevi in a single patient, Lanschuetzer et al observed melanoma-associated dermoscopic features that included a component pattern, an atypical pigment network, and irregular dots and globules in many of the patients in their EB registry. Even the milky red areas highly characteristic of melanoma were present in several of their nevi. When dermoscopic algorithms were performed, a false-positive score resulted in most of the lesions in their series. According to the authors,6 these apparently alarming clinical and dermoscopic findings can be explained by the known pathogenesis of EB nevi, ie, the repeated disruption of the dermoepidermal junction, fibrosing inflammation, scar formation, and neovascularization account for their clinical and dermoscopic features. Marghoob and Kopf7 have previously reported that a persistent melanocytic nevus frequently yields a false-positive dermoscopic score. It should be no surprise then that asymmetrical and irregularly pigmented EB nevi with a histopathologic pattern of persistent melanocytic neoplasm yield a false-positive dermoscopic score.

The histopathologic pattern of EB nevus ranges from the readily recognizable congenital pattern to a problematic persistent/pseudomelanoma pattern.1 2 Most persistent patterns occur in patients with recessive dystrophic EB, whereas the congenital pattern occurs more frequently in patients with EB simplex. Obviously, the fibrosing inflammation that is more frequently encountered in recessive dystrophic EB accounts for this observation. Some of the large lesions, even those with an ominous clinical appearance, display a banal compound congenital pattern, ie, monomorphous melanocytes in nests and fascicles spanning the papillary and reticular dermis with angiotropism and adenotropism.1 3 8 Other patients, like ours, have shown the persistent pattern, ie, uneven distribution of melanocytes within the epidermis and dermal melanocytes enveloped in fibrosis. The persistent pattern raises the differential diagnosis of persistent melanoma vs persistent melanocytic nevus. Diagnosing persistent nevus becomes problematic if sections from the previous procedure are not available and/or if only the portion of the persistent melanocytic neoplasm is biopsied, which may lack the readily recognizable conventional benign melanocytic pattern. In cases of large EB nevi, in which the entire lesion often cannot be sampled, the problem of the persistent pattern may not be resolvable on the basis of histologic sections alone because there are no previous sections to review and the entire lesion may not be available for review. Our patient represented such a dilemma. The clues that the lesion on our patient was benign included melanocytes in the dermis that were monomorphous, a lack of mitosis, and, accordingly, a normal proliferative index. In addition, the lesion in our patient had a striking clinical resemblance to a large superficial spreading melanoma, but this clinical and histopathologic pattern of melanoma, although common in adults, is exceedingly rare in children. Melanomas in children are usually papular or nodular and thus have a prominent vertical orientation clinically and histopathologically rather than the horizontal orientation that is typical of the superficial spreading type of melanoma.9 10 The knowledge of the EB nevus phenomenon and the histopathologic features eventually convinced us of the benign nature of the lesion on our patient.

Although it is obvious that the recurrent blisters and the subsequent inflammation and/or fibrosis alter the morphologic features of melanocytic nevi in patients with EB, the exact mechanism by which the recurrent blisters achieve the alteration is unknown. Speculations include (1) induction by the Koebner phenomenon, meaning that disruption of melanocytes at the site of blisters somehow induces proliferation during reepitheliazation,2 and (2) seeding of a blister cavity by melanocytes from a pre-existing nevus, which then proliferates owing to cytokines that are released by the inflammatory process caused by the blisters.8 Irrespective of the mechanism, the repeated blisters at the site of the nevi result in a dynamic growth pattern that may lead to clinical lesions, which may be asymmetrical and multicolored and have regressive changes due to chronic fibrosing inflammation rather than to specific immune-mediated process mounted against melanocytes.

An EB nevus represents a collision between an inflammatory disease and a melanocytic nevus that results in unconventional phenotypic expression of the nevus. Collision between lichen sclerosus et atrophicus and melanocytic nevus represents an analogous phenomenon.11 12 These collision phenomena have led to diagnostic difficulties for the clinicians and histopathologists because the expected clinical and histopathologic findings of the melanocytic lesions are significantly altered. Similar to the EB nevus, the persistent melanocytic pattern is observed histopathologically in cases of collision with lichen sclerosus.13 The well-
circumscribed nature of these lesions allows for correct interpretation in most instances. In cases of a large EB nevus, however, circumscription often cannot be assessed because only a portion of the lesion is available for interpretation. This adds to the diagnostic difficulty compared with the cases of lichen sclerosus. Previously reported cases of eruptive melanocytic nevi that appeared shortly after episodes of Stevens-Johnson syndrome and bullous erythema multiforme have been suggested as analogous phenomena. In these instances, there is no collision, per se; rather, the 2 phenomena occur metachronously rather than synchronously. Accordingly, diagnostic difficulties are not reported because there are no significant clinical and histopathologic alterations of the nevi's morphologic features. Curiously, analogous phenomena have not been reported with any frequency in other blistering diseases known to occur in childhood, such as linear IgA dermatosis. In 1 reported case of an 8-year-old girl with bullous pemphigoid of the vulva, a melanocytic lesion at the site of the blisters eventually regressed completely. As in our patient, the lesion resembled melanoma clinically and dermoscopically.

Although the association between squamous cell carcinoma and chronic scarring inflammatory dermatosis is well known, it is unclear whether such an association exists for melanoma in general. Data suggest that a higher incidence of melanoma may exist in patients with EB, especially recessive dystrophic EB, but there are no detailed, well-documented cases in the literature, in contrast to the well-documented and now well-known higher incidence of squamous cell carcinoma in patients with EB. Furthermore, the higher incidence has not been corroborated by experience in other countries. Because EB nevi may simulate melanoma, they have the potential to falsely increase the incidence and prevalence of melanoma among patients with EB if they are misconstrued as such. Clinicians and histopathologists should be aware of this phenomenon to avoid misdiagnosis and unnecessary therapeutic intervention. An EB nevus should be considered a distinct diagnostic possibility and should be excluded if melanoma is suspected in a child with EB. Once it has been established clinically, dermoscopically, and histopathologically that a lesion is an EB nevus, close clinical follow-up of these unconventional melanocytic nevi is an acceptable option, especially for nevi that are not amenable to simple excision owing to their large size.

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