OBSERVATION

Constitutional Intraepidermal Ascent of Melanocytes

A Potential Pitfall in the Diagnosis of Melanocytic Lesions

Katrin Kerl, MD; Werner Kempf, MD; Jivko Kamarashev, MD; Giulia Spallone, MD; Ralph Braun, MD; Thomas Wiesner, MD; Lars E. French, MD; Reinhard Dummer, MD

Background: Transepidermal melanocytic migration (TEM) is an important diagnostic criterion for malignancy, especially in association with cytologic atypia. However, TEM may also be observed in benign melanocytic tumors, such as Spitz nevus, acral nevi, or nevi in infancy. We discuss the value of TEM for the diagnosis of melanocytic tumors in a young patient previously diagnosed as having 11 cutaneous melanomas.

Observation: A 17-year-old patient with a history of 11 cutaneous melanomas diagnosed in the past 3 years by different expert dermatopathologists presented in our department. The previous histological diagnoses of melanoma were mainly based on the presence of important TEM. A reevaluation of all histological specimens in light of the clinical context and the lack of genomic aberrations as detected by array-comparative genomic hybridization led to a revision of the previous diagnoses. The striking TEM observed represents, in our opinion, a constitutional element of the melanocytic nevi in this patient and not a marker of malignancy.

Conclusion: Awareness of this finding is important to avoid overdiagnosis of melanoma in cases of melanocytic nevi.

Arch Dermatol. 2012;148(2):235-238

TRANSEPIDERMAL MIGRATION of melanocytes (TEM) is one of the hallmarks in the histological diagnosis of melanoma.[1-4] Although considered a conspicuous feature of malignancy in combination with cytologic atypia, TEM can be observed in certain variants of benign melanocytic lesions, such as Spitz nevi, acral or genital nevi, recurrent nevi, and nevi in infancy and in traumatized or sun-exposed melanocytic lesions.[5-8] Herein we discuss the value of TEM in the diagnosis of melanocytic lesions in the context of a special observation made in a 17-year-old girl with multiple melanocytic tumors.

REPORT OF A CASE

A 17-year-old girl presented to our department with 11 previous diagnoses of melanoma by various dermatopathologists and pathologists, including international experts. The first melanocytic lesion, localized on the lower back, was excised at 14 years of age and diagnosed histopathologically as a melanoma of the superficial spreading type with a Breslow thickness of 0.34 mm in combination with a congenital nevus. The diagnosis was based on the presence of striking TEM. During the subsequent 3-year period, clinically inconspicuous pigmented lesions were excised in the context of melanoma screening consultations. The biopsy specimens taken during these 3 years were sent to different dermatopathological laboratories. In total, 21 pigmented lesions were excised, of which an additional 10 showed notable TEM and were thus classified as melanoma.

The patient was referred to our department for review of her medical situation and follow-up. Given the youth of the patient and the clinically benign appearance of the lesions (**Figure 1**), doubt was raised about the previous histological diagnoses of melanomas. As a consequence, all previous biopsy specimens were collected and histological slides were individually and critically reevaluated by 4 senior board-certified dermatopathologists (K.K., W.K., J.K., and R.D.).

On clinical examination, the patient had a fair complexion (Fitzpatrick skin type II) with multiple lentigines and more than 100 small benign-looking melanocytic nevi (Figure 1A). At the sites of previous sur-

Author Affiliations: Departments of Dermatology, University Hospital of Zurich, Zurich, Switzerland (Drs Kerl, Kempf, Kamarashev, Braun, French, and Dummer), University Hospital of Rome, Rome, Italy (Dr Spallone), and Medical University of Graz, Graz, Austria (Dr Wiesner).

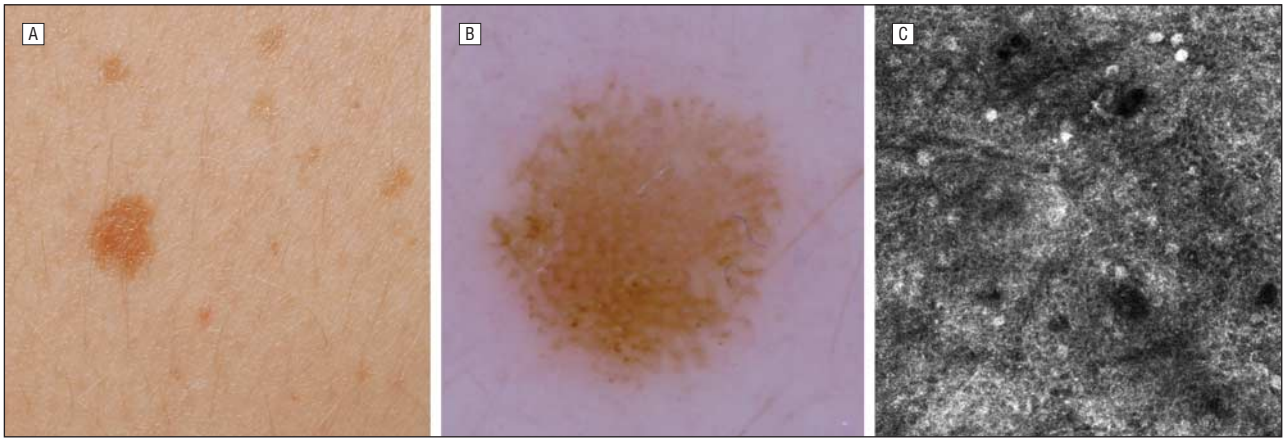

Figure 1. Melanocytic lesions in a 17-year-old girl. A, Representative clinical image of the lesions. B, Dermoscopic image shows a faint pigment network with numerous regular streaks at the periphery and hypopigmented roundish structures in the center (original magnification ×20). C, Confocal microscopic image of the lesion in part B shows a regular honeycomb pattern with the presence of numerous bright pagetoid cells in the superficial layers of the epidermis corresponding to transepidermal migration of melanocytes (original magnification ×40).

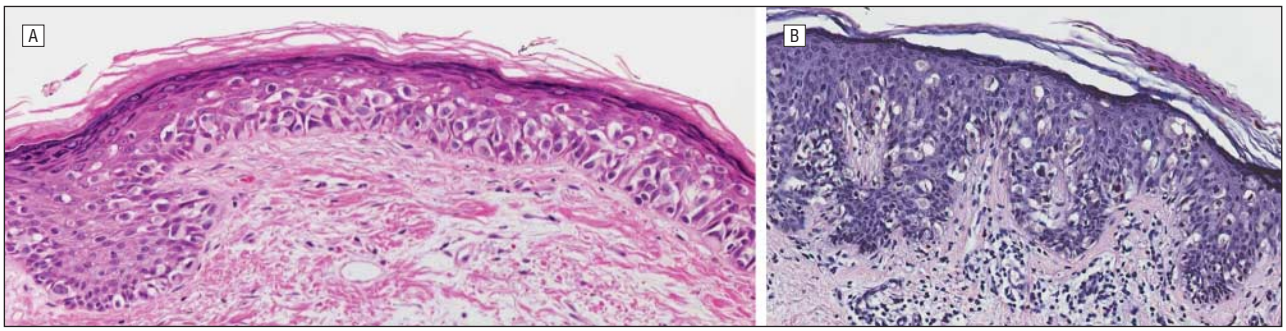

Figure 2. Comparison of melanoma and a melanocytic lesion. A, Typical example of a melanoma in situ. Pagetoid spread of melanocytes with abundant cytoplasm and atypical nuclei throughout the epidermis (hematoxylin-eosin, original magnification ×100). B, One of the patient's melanocytic lesions shows proliferation of melanocytes with scant cytoplasm, arranged in solitary units at the dermoepidermal junction and above it. Only the lack of significant nuclear atypia together with sharp borders and symmetry (not shown) may allow distinction from a melanoma in situ (hematoxylin-eosin, original magnification ×100).

gery, some hypertrophic scars were present. There was no family history of melanoma or dysplastic nevus syndrome. The patient reported occasional pruritus of selected pigmented lesions without any notable changes in their aspect. She did not report the recent appearance of new pigmented lesions.

Dermoscopic analysis of the pigmented skin lesions consistently revealed a faint pigment network with numerous regular streaks at the periphery and hypopigmented roundish structures in the center of the lesion (Figure 1B). Reflectance confocal microscopic analysis was performed on 7 pigmented lesions. All 7 lesions showed a similar aspect, notably a regular honeycomb pattern with the presence of numerous pagetoid cells in the epidermis (Figure 1C).

A total of 21 biopsy specimens of pigmented lesions excised during a 3-year period were analyzed histopathologically by the 4 dermatopathologists. Eleven of the 21 biopsy specimens had been previously classified as melanomas. These 11 biopsy specimens all exhibited very similar histological features, notably, small, fairly well-circumscribed intraepidermal melanocytic proliferations with a predominant single-cell component (**Figure 2** and **Figure 3**). Only few junctional nests could be detected in some specimens. The pagetoid spread of melanocytes was present in all layers of the epidermis, and involvement of the follicular epithelium was occasionally observed. Cytomorphological analysis revealed small nuclei with only slight atypia in most specimens. The cytoplasm of melanocytic cells was abundant and frequently vacuolized or foamy, and focally the intraepidermal melanocytes revealed spitzoid features.

In the first biopsy specimen excised when the patient was 14 years of age (Figure 3A), a large intradermal component with a significantly increased number of single melanocytes situated within the epidermis could be detected. In all the other specimens, the melanocytes were intraepidermal or only a few nests of melanocytes were found in the papillary dermis (Figure 3B and C).

All lesions showed immunohistochemical positivity of melanocytes for MelanA antibodies. Reactivity to HMB45 was mainly observed in the junctional components of the melanocytic lesions, and immunolabeling for p53, p16, and the melanoma-associated antigen[9] yielded negative findings.

To further analyze the molecular nature of the melanocytic lesions, epidermal nests of melanocytes of 2 lesions previously diagnosed as malignant melanoma (MM) underwent laser microdissection and analysis by array-comparative genomic hybridization,[10] a technique that permits analysis of the whole genome of a patient on a molecular genetic level and is considered to be a highly

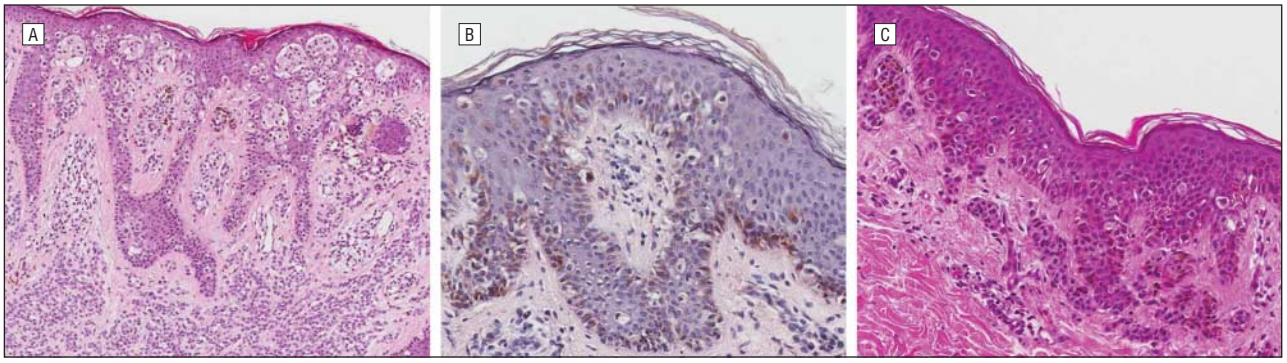

Figure 3. Examples of melanocytic nevi from serial excisions between 2007 and 2009. The striking transepidermal migration of melanocytes (TEM) led to the initial diagnosis of melanoma in 11 of the patient's melanocytic tumors. A, Nests and single units of TEM with small nuclei above an inconspicuous dermal component (hematoxylin-eosin, original magnification ×100). B, A melanocytic nevus with TEM (hematoxylin-eosin, original magnification ×100). C, Another example with the typical histological features of TEM that were observed in the patient's nevi (hematoxylin-eosin, original magnification ×100).

sensitive method to detect chromosomal aberrations indicative of malignancy. In a study by Bastian et al[11] in 2003, chromosomal aberrations were detected in 127 of 132 MM (96%) and in 7 of 54 nevi (13%). In the 2 lesions analyzed from our patient, no DNA copy number changes indicative of malignancy, notably gains or losses in chromosomal segments, were detected.

Taken together, the clinical presentation, dermoscopic, confocal microscopic, and histological features and the lack of DNA copy number changes as assessed by array-comparative genomic hybridization are all congruent and indicative of benign melanocytic lesions with striking and misleading intraepidermal ascent of melanocytes. The latter phenomenon occurring in multiple melanocytic lesions from the same patient in the absence of other histological signs of malignancy should be recognized and critically interpreted. Awareness of this finding is important to avoid overdiagnosis of MM in cases of melanocytic nevi.

COMMENT

The mechanisms leading to an upward spread of melanocytes within the epidermis seem to depend on the expression levels of cadherins (E-cadherin or N-cadherin) but are not yet fully understood.[12] Transepidermal migration of melanocytes is a characteristic sign of melanoma that can also be observed in various benign melanocytic lesions. Distinct biological processes can be responsible for the phenomenon.

In the case of MM, downregulation of adhesion molecules on the tumor cell population may allow transmigration. In benign melanocytic lesions, this process may be the result of loss of control of keratinocytic homeostasis during an inflammatory stress response. Trauma, UV radiation, or increased cell proliferation in the Spitz nevi or nevi in infancy may alter the adhesion of melanocytes to neighboring keratinocytes and basement membrane. Together with an altered expression of adhesion molecules and integrins, increased keratinocytic proliferation and/or apoptosis associated with inflammation may lead to an upward flow of melanocytes.

Among the histological criteria for melanoma, transepidermal migration (pagetoid spread) is one of the most important. Therefore, it is not surprising that several of the melanocytic lesions that displayed striking TEM of melanocytes in single units, sometimes in association with slight nuclear atypia and epithelioid cytomorphologic characteristics, were diagnosed first as MM in our patient. The unusually high number of melanomas in one individual, the patient's relative youth, and the clinically benign appearance of the multiple nevi, including dermoscopy—despite the documentation of transmigration by confocal microscopy—raised doubts about the diagnosis of multiple MM and led to the reevaluation of all biopsy specimens. The genetic studies performed also did not support a diagnosis of melanoma. Based on all these observations, TEM was reinterpreted in our patient as a constitutive element of her individual melanocytic nevi and not as a marker for MM.

The question arises as how to classify these nevi with striking TEM in a young patient. The differential diagnoses to be considered within the spectrum of melanoma simulators include multiple early Spitz nevi, pseudomelanoma in infancy, the recently described Spark nevi (Spitz nevus and Clark/dysplastic nevi), and de novo intraepidermal epithelioid melanocytic dysplasia.[13-15] Our observations cannot be clearly attributed to any of these various melanocytic proliferations. A diagnosis of multiple Spitz nevi can be ruled out because the cytological features of Spitz nevus were found only focally in a few specimens. In pseudomelanoma of infancy, a congenital intradermal nevus is present. In a small number of melanocytic lesions that were previously diagnosed as melanoma in our patient, we observed overlapping features with Spark nevus and de novo intraepidermal epithelioid melanocytic dysplasia. Clinically, however, atypical nevi were described in the cited reports concerning Spark and de novo intraepidermal epithelioid melanocytic dysplasia. These features were not present in our patient.

Multiple melanocytic nevi with benign clinical features and abundant TEM mimicking MM might therefore represent a distinct entity or syndrome. We propose to call this phenomenon *constitutional intraepidermal ascent of melanocytic cells* (CONIAC) analogous to the term *melanocytic acral nevi with intraepidermal ascent of cells* (MANIAC) coined by McCalmont et al[16] to de-

scribe TEM in acral nevi. We cannot predict at the moment whether this syndrome is associated with a higher risk for development of melanoma, similar to the dysplastic nevus syndrome. Only additional observations and long-term follow-up of a larger number of patients with this phenomenon will enable a better definition of this type of unusual melanocytic proliferation.

Our report is aimed at increasing awareness of this interesting finding and preventing misinterpretation of melanocytic nevi, thereby limiting the psychosocial and medical sequelae of overdiagnosing melanoma in such patients.

Accepted for Publication: October 3, 2011.
Correspondence: Katrin Kerl, MD, Department of Dermatology, University Hospital of Zurich, CH-8091 Zurich, Switzerland (katrin.kerl@usz.ch).
Author Contributions: All authors had full access to all the data presented in this manuscript and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Kerl, Kempf, Spallone, and Dummer. *Acquisition of data:* Kerl, Kempf, Braun, Wiesner, and Dummer. *Analysis and interpretation of data:* Kerl, Kempf, Kamarashev, Braun, Wiesner, French, and Dummer. *Drafting of the manuscript:* Kerl, Kempf, and Spallone. *Critical revision of the manuscript for important intellectual content:* Kempf, Kamarashev, Braun, Wiesner, French, and Dummer. *Obtained funding:* Dummer. *Administrative, technical, and material support:* Kempf, Wiesner, and Dummer. *Study supervision:* Spallone, French, and Dummer.
Financial Disclosure: None reported.
Funding/Support: This study was supported in part by the Gottfried and Julia Bangerter-Rhyner-Stiftung and G + B Schwyzer Stiftung.

REFERENCES

1. Petronic-Rosic V, Shea CR, Krausz T. Pagetoid melanocytosis: when is it significant? *Pathology.* 2004;36(5):435-444.
2. Urso C, Saieva C, Borgognoni L, Tinacci G, Zini E. Sensitivity and specificity of histological criteria in the diagnosis of conventional cutaneous melanoma. *Melanoma Res.* 2008;18(4):253-258.
3. Stern JB, Haupt HM. Pagetoid melanocytosis: tease or tocsin? *Semin Diagn Pathol.* 1998;15(3):225-229.
4. Massi G, Le Boit Ph. *Histologic Diagnosis of Nevi and Melanoma.* New York, NY: Springer-Verlag; 2004.
5. Hosler GA, Moresi JM, Barrett TL. Nevi with site-related atypia: a review of melanocytic nevi with atypical histologic features based on anatomic site. *J Cutan Pathol.* 2008;35(10):889-898.
6. Gleason BC, Hirsch MS, Nucci MR, et al. Atypical genital nevi: a clinicopathologic analysis of 56 cases. *Am J Surg Pathol.* 2008;32(1):51-57.
7. Requena C, Requena L, Kutzner H, Sánchez Yus E. Spitz nevus: a clinicopathological study of 349 cases. *Am J Dermatopathol.* 2009;31(2):107-116.
8. Hoang MP, Prieto VG, Burchette JL, Shea CR. Recurrent melanocytic nevus: a histologic and immunohistochemical evaluation. *J Cutan Pathol.* 2001;28(8):400-406.
9. Hofbauer GF, Schaefer C, Noppen C, et al. MAGE-3 immunoreactivity in formalin-fixed, paraffin-embedded primary and metastatic melanoma: frequency and distribution. *Am J Pathol.* 1997;151(6):1549-1553.
10. Bauer J, Bastian BC. Distinguishing melanocytic nevi from melanoma by DNA copy number changes: comparative genomic hybridization as a research and diagnostic tool. *Dermatol Ther.* 2006;19(1):40-49.
11. Bastian BC, Olshen AB, LeBoit PE, Pinkel D. Classifying melanocytic tumors based on DNA copy number changes. *Am J Pathol.* 2003;163(5):1765-1770.
12. Hsu MY, Meier FE, Nesbit M, et al. E-cadherin expression in melanoma cells restores keratinocyte-mediated growth control and down-regulates expression of invasion-related adhesion receptors. *Am J Pathol.* 2000;156(5):1515-1525.
13. Boone SL, Busam KJ, Marghoob AA, et al. Two cases of multiple Spitz nevi: correlating clinical, histologic, and fluorescence in situ hybridization findings. *Arch Dermatol.* 2011;147(2):227-231.
14. Ko CJ, McNiff JM, Glusac EJ. Melanocytic nevi with features of Spitz nevi and Clark's/dysplastic nevi ("Spark's" nevi). *J Cutan Pathol.* 2009;36(10):1063-1068.
15. Magro CM, Crowson AN, Mihm MC, Kline M. De novo intraepidermal epithelioid melanocytic dysplasia: an emerging entity. *J Cutan Pathol.* 2010;37(8):866-869.
16. McCalmont TH, Brinsko R, LeBoit PE. Melanocytic acral nevi with intraepidermal ascent of cells (MANIAC's): a reappraisal of melanocytic lesions from acral sites [abstract]. *J Cutan Pathol.* 1991;18(5):378.