The role of reflectance confocal microscopy in differentiating melanoma in situ from dysplastic nevi with severe atypia: A cross-sectional study

Naiara Fraga-Braghiroli, MD,[a] Jane M. Grant-Kels, MD,[b,c] Margaret Oliviero, ARNP,[d] Harold Rabinovitz, MD,[d] Katalin Ferenczi, MD,[b] and Alon Scope, MD[e]
Miami, Gainesville, and Plantation, Florida; Farmington, Connecticut; and Tel Aviv, Israel

Background: Melanoma in situ and dysplastic nevi with severe atypia present overlapping histopathologic features. Reflectance confocal microscopy findings can be integrated with the dermatopathology report to improve differentiation between melanoma and dysplastic nevi with severe atypia.

Objective: To compare prevalence of reflectance confocal microscopy findings between melanoma in situ and dysplastic nevi with severe atypia.

Methods: This retrospective observational study compared reflectance confocal microscopy findings in dermatopathologically diagnosed dysplastic nevi with severe atypia and melanoma in situ, collected between 2007 and 2017 at a private pigmented-lesion clinic. Concordant pathologic diagnosis was defined as unanimous agreement between 3 dermatopathologists who independently reviewed all cases; all other cases were classified as discordant.

Results: The study included 112 lesions, 62 concordant melanomas in situ, 28 concordant dysplastic nevi with severe atypia, and 22 discordant lesions. In comparing reflectance confocal microscopy findings in concordant cases, melanoma in situ showed more frequently than dysplastic nevi with severe atypia the presence of epidermal atypical melanocytes as round cells (19/62 vs 0/28; $P < .001$) and dendritic cells (50/62 vs 6/28; $P < .001$), as well as a diffuse distribution of epidermal atypical melanocytes (50/54 vs 3/6; $P = .002$). In contrast, dysplastic nevi with severe atypia showed the presence of dense melanocytic nests more frequently than melanoma in situ did (15/28 vs 14/62; $P = .003$).

Limitations: The study was based on a limited number of lesions originating from a single clinic.

Conclusions: Reflectance confocal microscopy findings may help differentiate a subset of dysplastic nevi with severe atypia from melanoma in situ. (J Am Acad Dermatol 2020;83:1035-43.)

Key words: confocal microscopy; dermatopathology; dysplastic nevi; melanoma; severe atypia; skin imaging.

From Miami Cancer Institute, Dermatology[a]; University of CT Dermatology Department, Farmington[b]; University of Florida Dermatology Department, Gainesville[c]; Skin Cancer & Associates, Dermatology, Plantation[d]; and The Kittner Skin Cancer Screening & Research Institute, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University.[e]

Funding sources: None.
Conflicts of interest: Dr Rabinovitz is a consultant and has received equipment from 3-Gen, manufacturer of a polarized dermatoscope. Drs Fraga-Braghiroli, Grant-Kels, Ferenczi, and Scope and Author Oliviero have no conflicts of interest to declare.

IRB approval status: Reviewed and approved by the University of Miami institutional review board (45CFR46).
Accepted for publication May 12, 2020.
Reprints not available from the authors.
Correspondence to: Naiara Fraga-Braghiroli, MD, Miami Cancer Institute, Dermatology, 8900 North Kendal Dr, Miami, FL 33176. E-mail: nfbraghiroli@gmail.com.
Published online May 19, 2020.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.05.071

INTRODUCTION

Dysplastic nevi have been the subject of controversy.[1-5] They were originally clinically described as nevi with a diameter greater than 5 mm, ill-defined borders, variegated color, and a macular component in the context of patients with family or personal history of melanoma and multiple nevi.[1,2,6-10] They have been associated with variable histopathologic findings, including junctional nests extending laterally beyond the dermal component, architectural asymmetry, epidermal melanocytic cytologic atypia, and nests of junctional melanocytes with different size and shapes irregularly disposed along and between the rete ridges.[8,11,12] Dysplastic nevi have been associated with an increased melanoma risk.[13-18] A meta-analysis found a relative risk for melanoma of 6.4 (confidence interval 3.8-10.3) for individuals with greater than or equal to 5 dysplastic nevi compared with those without them.[19]

CAPSULE SUMMARY

- Melanoma in situ and dysplastic nevus with severe atypia present overlapping dermatopathologic features. Reflectance confocal microscopy may be integrated with the histopathologic report to improve differentiation between these entities.
- Confocal finding of epidermal round or dendritic cells, particularly when diffuse, favors a diagnosis of melanoma in situ over dysplastic nevus with severe atypia.

Many dermatopathologists report dysplastic nevi with qualitative grading of cytologic atypia as mild, moderate, or severe[9,20,21]; this grading system has been scrutinized as having low interobserver reproducibility.[22] However, higher-grade dysplastic nevi may present overlapping features with melanoma in situ, and the diagnoses of moderate or severe dysplastic nevi versus early-stage melanoma has also shown low interrater reproduciblity.[23] In recognition of these limitations of pathologic diagnosis, high-grade dysplastic nevi entail clinical management recommendations such as ensuring clear excisional margins.[24-26] Clinicians integrate their bedside evaluation of the lesion with the subsequent histopathologic findings in forming their management decisions.[27-29]

Reflectance confocal microscopy is a bedside, noninvasive, cellular-level, resolution imaging technology that allows clinicians to further increase their clinical accuracy. It uses an 830-nm laser to generate horizontal optical sections of skin, with lateral resolution of 1 to 3 μm, depth of penetration of 250 μm (reaching the papillary dermis), and field of view of up to 8 × 8 mm^2. A systematic review found a sensitivity of 93% and specificity of 76% for the reflectance confocal microscopy diagnosis of melanoma.[30] Reflectance confocal microscopy findings correlate well with histopathologic criteria.[31] Hence, such microscopy has the potential to help the clinician formulate a microscopic diagnosis at the bedside, which can later be integrated with—and help scrutinize—the histopathologic report. This can be particularly useful in managing challenging cases such as high-grade dysplastic nevi. To this end, the primary aim of the present study was to compare prevalence of reflectance confocal microscopy criteria between dysplastic nevi with severe atypia and melanoma in situ.

MATERIALS AND METHODS

This retrospective observational study compared dermatopathologically diagnosed dysplastic nevi with severe atypia and melanoma in situ data collected from July 2007 to June 2017 at a private practice specializing in skin cancer screening.

For included cases, the following data were required: demographic and clinical data, including the patient's age and sex and lesion's anatomic location and longest diameter; a digital dermoscopic image; reflectance confocal microscopy mosaic images (field of view of up to 8 × 8 mm^2) acquired with a wide-probe reflectance confocal microscopy device (Vivascope1500, Caliber Imaging & Diagnostics, Andover, MA) in standardized fashion at 3 anatomic levels: mid epidermis, basal layer/dermal-epidermal junction, and papillary dermis; and original histopathologic diagnosis of melanoma in situ or dysplastic nevi with severe atypia by a board-certified dermatopathologist and slides available for pathologic review.

Three reflectance confocal microscopy–proficient readers (N.F.B., M.O., and H.R.), who were blinded to the pathologic diagnosis, reviewed the reflectance confocal microscopy images. They evaluated the presence of predefined reflectance confocal microscopy criteria (Table I). For the presence of round nucleated cells, dendritic-shaped cells, or both at mid epidermis, at least 3 cells needed to be identified to be considered a positive finding.

In addition to the original dermatopathologist's diagnosis issued at biopsy, all cases were reevaluated as unknowns, using scanned digital whole slides, by 2 additional board-certified dermatopathologists (J.M.G.-K. and K.F.). Each reader classified lesions as melanoma in situ or dysplastic nevi with severe atypia; when a dermatopathologist was uncertain

Table I. Comparison of reflectance confocal microscopy features between melanoma in situ and dysplastic nevi with severe atypia

	Concordant			Discordant		
Reflectance confocal microscopy features	**MMIS, No. (%)**	**DNSA, No. (%)**	***P* value value**	**MMIS, No. (%)**	**DNSA, No. (%)**	***P* value**
Presence of atypical melanocytes						
Sample size, n	62	28		5	17	
Dendritic	50 (80.6)	6 (21.4)	<.001	5 (100)	10 (58.8)	.08
Round	19 (30.6)	0	<.001	1 (20.0)	2 (11.8)	.64
None	8 (12.9)	22 (78.5)	<.001	0	7 (41.1)	.08
Location and density of atypical melanocytes						
Sample size, n	54	6		5	10	
Stratum corneum and spinous-granular	54 (100)	5 (83.3)	.86	5 (100)	3 (30.0)	.01
DEJ	41 (75.9)	6 (100)	.002	5 (100)	10 (100)	—
Central	0	3 (50.0)	.17	0	0	—
Peripheral	0	0	—	0	4 (40.0)	.098
Diffuse	50 (92.5)	3 (50.0)	.002	5 (100)	6 (60.0)	.097
Density 3−6	4 (7.4)	1 (16.7)	.44	0	2 (20.0)	.28
Density >6	50 (92.6)	5 (83.3)		5 (100)	8 (80.0)	
Architectural features						
Sample size, n	62	28		5	17	
Honeycomb typical	27 (43.5)	16 (57.1)	.23	0	13 (76.5)	.002
Honeycomb atypical	25 (40.3)	4 (14.3)	.01	3 (60.0)	2 (11.8)	.02
Cobblestone typical	0	4 (14.3)	.002	0	2 (11.8)	.42
Cobblestone atypical	3 (4.8)	4 (14.3)	.12	2 (40.0)	0	.006
Bright cells at the epidermis/DEJ	42 (67.7)	17 (60.7)	.52	4 (80.0)	12 (70.6)	.67
Ring pattern typical	1 (1.6)	3 (10.7)	.05	0	1 (5.9)	.58
Ring pattern atypical	1 (1.6)	3 (10.7)	.05	0	1 (5.9)	.58
Meshwork typical	5 (8.1)	3 (10.7)	.68	0	3 (17.6)	.31
Meshwork atypical	41 (66.1)	15 (53.6)	.26	3 (60.0)	11 (64.7)	.85
Mixed pattern	4 (6.5)	1 (3.6)	.58	2 (40.0)	1 (5.9)	.05
Junctional thickening	38 (61.3)	15 (53.6)	.49	2 (40.0)	13 (76.5)	.12
Milialike cyst	12 (19.4)	7 (25.0)	.54	2 (40.0)	3 (17.6)	.29
Dense nest at DEJ or papillary dermis	14 (22.6)	15 (53.6)	.003	1 (20.0)	8 (47.1)	.28

P values correspond to χ^2 tests or Fisher's exact test.
DEJ, Dermal-epidermal junction; *DNSA*, dysplastic nevi with severe atypia; *MMIS*, malignant melanoma in situ; —, not statistically significant.

about diagnosis but could not rule out melanoma in situ, diagnosis was reported as the pathologist would sign out in practice (eg, atypical melanocytic hyperplasia or proliferation). All 3 dermatopathologists were trained at different institutions and reviewed the cases independently.

Statistical analysis

IBM SPSS was used to analyze the data (version 24, IBM Corp, Armonk, NY). Descriptive statistics explored characteristics of participants according to the diagnosis of melanoma in situ or dysplastic nevi with severe atypia. Concordance was defined as agreement between all 3 pathologists on 1 diagnosis (melanoma in situ or dysplastic nevi with severe atypia); all other cases were classified as discordant. χ^2 Test or Fisher's exact test was used to assess concordance and discordance rate on different characteristics of melanoma in situ and dysplastic nevi with severe atypia. Statistical significance was set at $P < .05$.

RESULTS

Demographics and clinical data

The study included 112 lesions, 45 originally diagnosed as dysplastic nevi with severe atypia and 67 as melanoma in situ. Based on the original pathologic classification, mean age at diagnosis was 48.9 years (range 20-75 years; standard deviation 14.4 years) for dysplastic nevi with severe atypia and 67.8 years (range 29-88 years; standard deviation 10.5 years) for melanoma in situ; 58% of dysplastic nevi with severe atypia versus 70% of melanoma in situ occurred in men. The mean size was 5.4 mm (range 1-10 mm) for dysplastic nevi with severe atypia versus 9 mm (range 2-25 mm) for melanoma

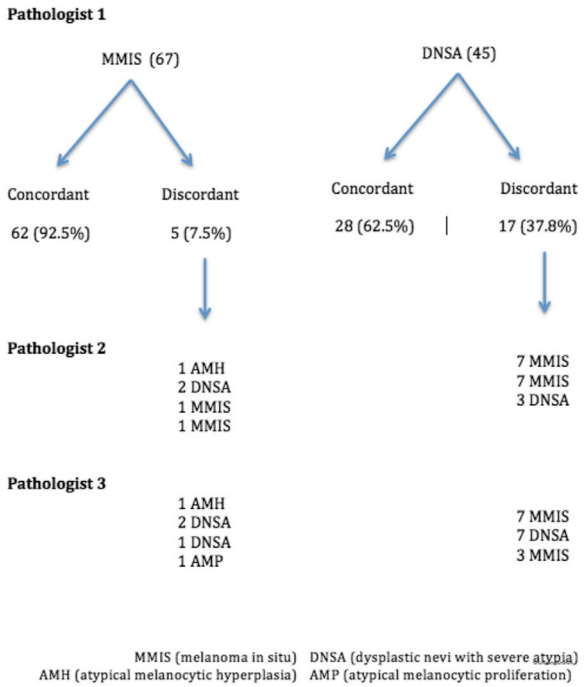

Fig 1. Distribution of diagnoses by the 3 dermatopathologists.

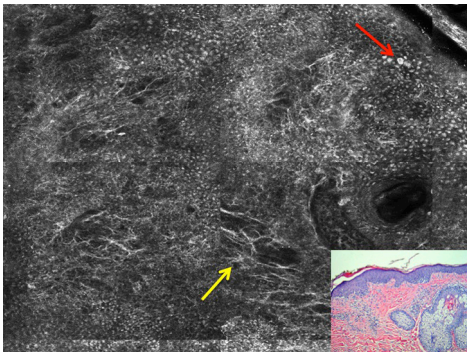

Fig 2. Concordant melanoma in situ. Reflectance confocal microscopy mosaic (1 × 1 mm^2) at the spinous and basal layers showing an overall nonspecific pattern, with round nucleated cells in pagetoid spread (red arrow) and diffuse proliferation of dendritic cells as sheets (yellow arrow). Inset of corresponding histopathology displays nests of melanocytes at the dermal-epidermal junction that vary in size and shape, demonstrate bridging with adjacent nests, and extend down adnexal structures. There is irregular junctional lentiginous single atypical melanocytic hyperplasia at the dermal-epidermal junction, as well as in a pagetoid distribution in the upper epidermis. (**Inset**, Hematoxylin-eosin stain; original magnification: ×100.)

in situ. The distribution of anatomic sites of dysplastic nevi with severe atypia versus melanoma in situ was head and neck, 4 (8.8%) versus 22 (32.8%); trunk, 30 (66.6%) versus 29 (43.2%); upper extremities, 6 (13.3%) versus 10 (14.9%); and lower extremities, 5 (11.1%) versus 6 (9.0%).

Histopathology findings

There was overall diagnostic concordance among all 3 dermatopathologists in 90 of the 112 lesions (80.3%). The distribution of diagnoses among the 3 dermatopathologists is shown in Fig 1.

We compared diagnostic concordance by anatomic site. Among head and neck lesions, all 22 originally diagnosed as melanoma in situ received a concordant diagnosis by the 2 other dermatopathologists, whereas all 4 originally diagnosed dysplastic nevi with severe atypia received a discordant diagnosis. Comparing non–head and neck lesions (ie, trunk and extremities combined), 45 of 40 lesions (88.8%) originally diagnosed as melanoma in situ received a concordant diagnosis by the 2 other dermatopathologists, whereas only 28 of 41 lesions (68.2%) originally diagnosed as dysplastic nevi with severe atypia showed concordance.

Reflectance confocal microscopy findings

A comparison of reflectance confocal microscopy findings between dysplastic nevi with severe atypia and melanoma in situ is shown in Table I.

Among concordant melanoma in situ (Fig 2), 54 of 62 (87.1%) showed epidermal atypical melanocytes (dendritic or round cells) compared with only 6 of 28 (21.4%) among concordant dysplastic nevi with severe atypia ($P < .001$) (Fig 3). Round melanocytes were observed among 19 of 62 (30.6%) concordant melanomas in situ compared with none of 28 concordant dysplastic nevi with severe atypia ($P < .001$). Among concordant cases that showed epidermal atypical melanocytes, a diffuse distribution of the atypical melanocytes was observed in 50 of 54 (92.5%) among melanoma in situ versus 3 of 6 (50%) among dysplastic nevi with severe atypia ($P = .002$). Dense melanocytic nests were also more prevalent among dysplastic nevi with severe atypia (15/28, 53.6%) compared with melanoma in situ (14/62, 22.6%; $P = .003$); among these 14 melanomas in situ, the dense nests were junctional in 13 and dermal in 1 case of melanoma in situ associated with a nevus. In addition, among concordant cases, typical cobblestone pattern of the epidermis was observed among 4 of 28 dysplastic nevi with severe atypia (14.3%) compared with none of 62 melanomas in situ ($P = .002$).

Among discordant cases, the presence, location, and density of epidermal atypical melanocytes did not significantly differ between discordant melanoma in situ versus dysplastic nevi with severe

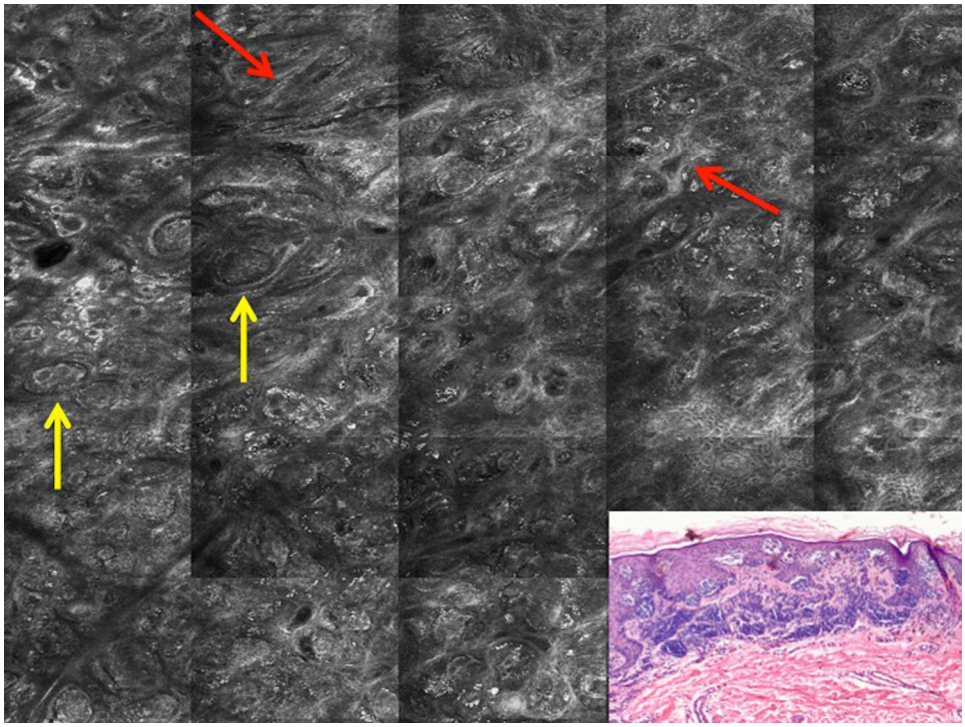

Fig 3. Concordant dysplastic nevus with severe atypia. Reflectance confocal microscopy mosaic (2.5 × 2.5 mm^2) at the dermal-epidermal junction showing an overall meshwork and clods pattern. The meshwork shows some variability in the thickness and brightness of the interpapillary spaces (retia, red arrows). There are junctional and dermal nests (yellow arrows). The spinous and granular layers showed typical honeycomb without atypical melanocytes (image not shown). Inset of corresponding histopathology displays single and nested melanocytic hyperplasia at the dermal-epidermal junction. Some discohesion of junctional melanocytic nests is identified but there is no pagetoid spread of melanocytes or nests extending down adnexa. There is underlying papillary dermal lamellar fibrosis with a lymphohistiocytic inflammatory infiltrate. No dermal nests of nevus cells are present on this section. (**Inset**, Hematoxylin-eosin stain; original magnification: ×100.)

atypia. Typical honeycomb was more prevalent among discordant dysplastic nevi with severe atypia (Fig 4), whereas atypical honeycomb and atypical cobblestone were more prevalent among discordant melanomas in situ.

Because on the head and neck area melanoma in situ on sun-damaged skin (lentigo maligna) is more prevalent, whereas dysplastic nevi with severe atypia are infrequent, we also performed subgroup analysis comparing reflectance confocal microscopy features between non–head and neck sites (Supplemental Table I, available via Mendeley at https://doi.org/10.17632/dd7nmk3sgr.2). The main aforementioned findings were confirmed. Among concordant melanoma in situ cases, 33 of 40 (82.5%) showed atypical melanocytes compared with 6 of 28 (21.4%) among concordant dysplastic nevi with severe atypia ($P < .001$). Round melanocytes were observed in 10 of 40 (25.0%) concordant melanomas in situ and in none of 28 concordant dysplastic nevi with severe atypia ($P = .004$). Among concordant cases that showed epidermal atypical melanocytes, a diffuse distribution was observed in 32 of 33 (96.9%) melanomas in situ compared with 3 of 6 (50%) dysplastic nevi with severe atypia ($P < .001$).

DISCUSSION

Interobserver agreement on histopathologic differentiation between melanoma in situ and dysplastic nevi with severe atypia is lacking. In the present study, only 80% of the lesions received a uniform diagnosis by all 3 dermatopathologists; in particular, concordance was notably lower for lesions originally diagnosed as dysplastic nevi with severe atypia (62.2%) than for those originally diagnosed as melanoma in situ (92.5%).

These limitations have led dermatopathologists to create a simplified ontology of histopathologic

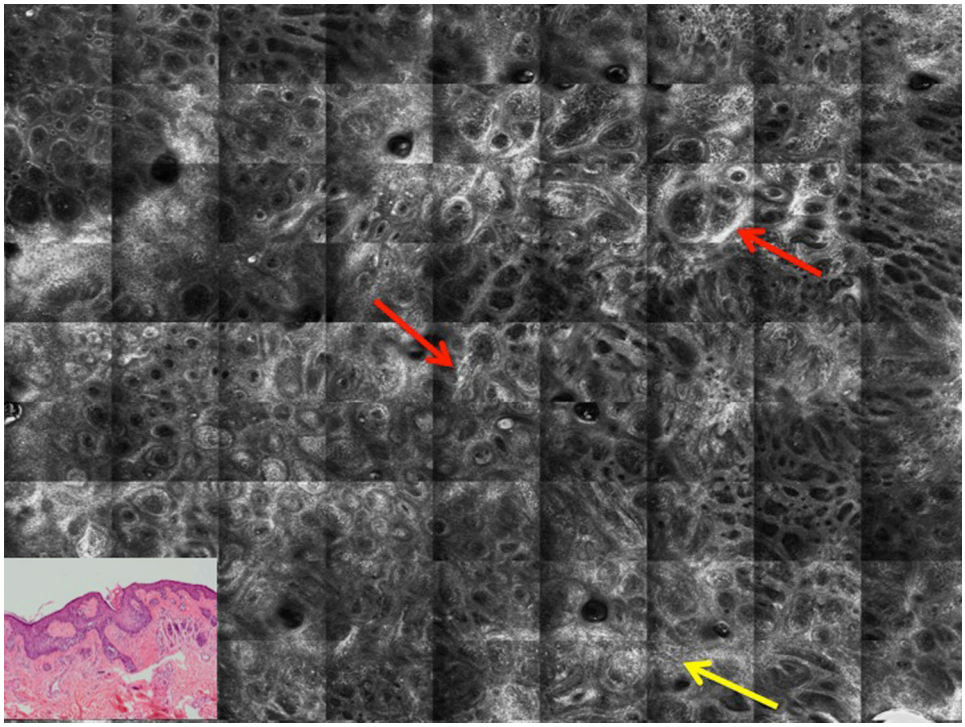

Fig 4. Discordant dysplastic nevus with severe atypia. Reflectance confocal microscopy mosaic (4.5 × 4.5 mm^2) at the dermal-epidermal junction showing an overall irregular meshwork pattern. The meshwork marked variability in the thickness and brightness of the interpapillary spaces (retia). There are poorly formed, irregularly shaped junctional aggregates of dendritic melanocytes (red arrows), as well as foci showing a proliferation of dendritic melanocytes as solitary units (yellow arrow). The dermal papillae show increased reticulated collagen. Inset of corresponding histopathology displays single and aggregated melanocytic hyperplasia at the dermal-epidermal junction, as well as focally some melanocytes noted above the dermal-epidermal junction, in a pagetoid distribution. There are junctional discohesive nests that vary in size and shape and nests extending down adnexal structures. In the underlying dermis there are nests of melanocytic nevus cells and melanophages. (**Inset**, Hematoxylin-eosin stain; original magnification: ×100.)

diagnosis of melanocytic neoplasms, termed Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis.[32,33] The tool's class III category encompasses melanoma in situ and dysplastic nevi with severe atypia. According to this scheme, lesions classified into class III are at higher risk for local tumor progression and should be managed by complete excision with at least 5-mm but less than 10-mm margins. Reproducibility among experienced pathologists was low in cases interpreted as class III, both for intraobserver (60%) and interobserver agreement (45%).[23]

Interobserver agreement can be further confounded by underlying patient characteristics. Braun et al[34] evaluated 1249 clinically equivocal melanocytic neoplasms; interobserver agreement among pathologists was significantly better for patients aged 40 years or older (κ = 0.67) than for younger patients (κ = 0.49). In addition, agreement was significantly lower for patients with atypical mole syndrome (κ = 0.31) than for patients without it (κ = 0.76). For patients with atypical mole phenotype and a personal or family history of melanoma, Sachdeva et al[35] described a series of 75 equivocal melanocytic neoplasms; the histologic hallmark of these lesions was a pagetoid spread of moderately to severely atypical epithelioid melanocytes within the epidermis. The authors emphasized the diagnostic difficulty associated with lesions that "defy classification as a dysplastic melanocytic nevus, but in which the morphologic features fall short of a diagnosis of melanoma in situ."

Because of the inherent limitations of stand-alone pathologic diagnosis, previous studies have shown that integrating pertinent clinical data into pathologic assessment can increase diagnostic concordance and

accuracy among pathologists. Ferrara et al[36] circulated histopathologic specimens from 99 clinically atypical melanocytic neoplasms among 10 pathologists. They showed that interobserver agreement on the diagnosis of nevus versus melanoma significantly increased, from κ = 0.57 for pathologic diagnosis blinded to any additional information to 0.64 when patients' age and sex and lesions' location were available, and to 0.67 when dermoscopic and clinical images were available; this trend was accompanied by a significant increase in pathologists' diagnostic confidence. Finally, Longo et al[37] showed the value of pathologic reappraisal in cases that lack clinical-dermoscopic-pathologic correlation; of 127 reevaluated melanocytic lesions, in 12 (9.4%) the pathologist changed the diagnosis from nevus to melanoma after being given more clinical data. Similarly, Shahriari et al[38] reported on a case series whereby prebiopsy reflectance confocal microscopy examination allowed a critical appraisal of histopathologic diagnosis that was discordant; in 4 cases showing reflectance confocal microscopy features of melanoma, pathologic diagnosis was revised from nevus to melanoma.

We anticipate that reflectance confocal microscopy evaluation may be integrated with the other bedside clinical data when one decides about both the diagnosis and management of melanocytic neoplasms with less than definitive histopathologic criteria.[38] Herein, we compared the reflectance confocal microscopy features of melanoma in situ and dysplastic nevi with severe atypia and found significant differences. Among cases that showed diagnostic concordance between 3 dermatopathologists, epidermal atypical melanocytes as round or dendritic cells, as well as diffuse distribution of epidermal atypical melanocytes, were more prevalent among melanomas in situ than dysplastic nevi with severe atypia. In fact, round melanocytes may be a melanoma-specific criterion; it was observed only among concordant melanoma in situ cases and in none of the concordant dysplastic nevi with severe atypia. On the other hand, the presence of dense nests and a typical cobblestone pattern were "protective features" more prevalent among dysplastic nevi with severe atypia than melanoma in situ.

Our findings are in line with those of previous reflectance confocal microscopy studies. Pellacani et al[39] compared the reflectance confocal microscopy features of 27 dysplastic nevi and 14 melanomas. The presence of widespread pagetoid infiltration, diffuse cytologic atypia at the dermal-epidermal junction, and nonedged papillae in greater than 10% of the lesion suggested the diagnosis of melanoma. Concerning reflectance confocal microscopy features were also positively correlated with histopathologically higher grading of dysplastic nevi: 40% of dysplastic nevi showed large nucleated cells in pagetoid distribution and 26% showed round cells; however, the atypical melanocytes in dysplastic nevi were mostly located at the lesion's center. Borsari et al[40] compared the reflectance confocal microscopy features of 120 melanomas in situ and 213 nevi. Significant reflectance confocal microscopy predictors of melanoma in situ were atypical melanocytes in pagetoid spread (odds ratio 2.8) and atypical melanocytes at the dermal-epidermal junction (odds ratio 8.4 if widespread and 3.4 if focal). On the other hand, the presence of dense nests and melanophages was inversely associated with melanoma in situ. Finally, Segura et al[41] found that the presence of typical basal cells (equivalent to typical cobblestone pattern in the present study) was a "protective criterion" favoring the reflectance confocal microscopy diagnosis of nevus, whereas the presence of roundish melanocytes in the suprabasal epidermis favored diagnosis of melanoma.

Our study also highlights cases of dysplastic nevi with severe atypia that are more likely to display pathologic interobserver discordance; under reflectance confocal microscopy, these discordant dysplastic nevi with severe atypia are more likely to demonstrate the presence of epidermal atypical melanocytes, including round cells. These concerning dysplastic nevi with severe atypia show greater reflectance confocal microscopy overlap with melanoma in situ, and should be flagged for rereview by dermatopathology. In addition, all of the head and neck cases originally diagnosed as dysplastic nevi with severe atypia were discordant; the diagnosis of dysplastic nevi with severe atypia on sun-damaged skin of the head and neck area warrants a rereview by dermatopathology.

These data suggest that lesions diagnosed as dysplastic nevi with severe atypia are not a uniform group and that this variability may influence management recommendations. Indeed, Engeln et al[26] challenged the notion that all dysplastic nevi with severe atypia need to be re-excised. They retrospectively analyzed 451 adult patients with dysplastic nevi with severe atypia and found that only 165 (67%) underwent re-excision of the biopsy site, and of those, 2 melanomas (1.2%; 1 melanoma in situ and 1 melanoma 0.3 mm thick) were subsequently found in the re-excision. Among 390 patients with dysplastic nevi with severe atypia and without history of melanoma, of whom one-third had a re-excision and two-thirds did not, none developed metastatic melanoma or developed a melanoma at the original biopsy site. The authors concluded that

re-excision of all dysplastic nevi with severe atypia may not be necessary.[26] They reasoned that clinical and dermoscopic factors likely affected the clinicians' decision regarding re-excision. In the future, clinicians may also integrate reflectance confocal microscopy data when deciding about definitive management of dysplastic nevi with severe atypia.

What is the relationship between the various dysplastic nevi with severe atypia and melanoma in situ? Conceivably, there are 3 options, not mutually exclusive. First, dysplastic nevi with severe atypia may represent a phase in the life of a benign nevus that simulates melanoma; for example, a severely traumatized or inflamed nevus. Second, some so-called dysplastic nevi with severe atypia may represent de novo early-evolving melanomas in situ that have not yet manifested the host of melanoma-specific criteria, and hence fall short of a malignant diagnosis. Third, some of these cases may be nevi that are undergoing malignant transformation into bona fide melanomas. We believe that integrating clinical, reflectance confocal microscopy, and histopathologic features may help to elucidate this quandary.

Our study has limitations. First, it is based on a limited number of lesions. Second, the study data set originated from a single pigmented-lesion clinic specializing in skin cancer diagnosis; this risks a referral bias that limits the generalizability of our findings. Third, the inherent lack of gold standard risks misclassification bias. We believe that the fact that 3 pathologists independently reviewed each case mitigated this bias. Fourth, the retrospective design of the study risks observer and selection bias. In addition, the 80% concordance rate between the 3 dermatopathologists is relatively high and may relate to shared biases; we tried to minimize this risk by including dermatopathologists who trained in separate institutions and by performing independent reading of the cases.

In conclusion, the findings of reflectance confocal microscopy examination may be useful in critically reviewing diagnoses of dysplastic nevi with severe atypia and melanoma in situ; the presence of diffusely distributed, epidermal round cells or dendritic cells is a red flag for the diagnosis of a melanoma in situ, rather than dysplastic nevi with severe atypia. In the face of the relatively high discordance rates associated with the diagnosis of dysplastic nevi with severe atypia, the current management recommendation for dysplastic nevi with severe atypia—excision with 5-mm clinical margins—is likely appropriate. Our findings need to be confirmed by a larger prospective study that will compare the clinical-dermoscopic-reflectance confocal microscopy findings in histopathologically diagnosed dysplastic nevi with severe atypia versus melanoma in situ.

REFERENCES

1. Clark WH Jr, Reimer RR, Greene M, Ainsworth AM, Mastrangelo MJ. Origin of familial malignant melanomas from heritable melanocytic lesions. 'The B-K mole syndrome'. *Arch Dermatol*. 1978;114(5):732-738.
2. Elder DE, Goldman LI, Goldman SC, Greene MH, Clark WH Jr. Dysplastic nevus syndrome: a phenotypic association of sporadic cutaneous melanoma. *Cancer*. 1980;46(8):1787-1794.
3. Ackerman AB, Mihara L. Dysplasia, dysplastic melanocytes, dysplastic nevi, the dysplastic nevus syndrome, and the relation between dysplastic nevi and malignant melanomas. *Hum Pathol*. 1985;16(1):87-91.
4. Ackerman AB. What naevus is dysplastic, a syndrome and the commonest precursor of malignant melanoma? a riddle and an answer. *Histopathology*. 1988;13(3):241-256.
5. Roesch A, Burgdorf W, Stolz W, Landthaler M, Vogt T. Dermatoscopy of "dysplastic nevi": a beacon in diagnostic darkness. *Eur J Dermatol*. 2006;16(5):479-493.
6. Greene MH, Clark WH Jr, Tucker MA, Kraemer KH, Elder DE, Fraser MC. High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. *Ann Intern Med*. 1985;102(4):458-465.
7. Barnhill RL. Current status of the dysplastic melanocytic nevus. *J Cutan Pathol*. 1991;18(3):147-159.
8. Barnhill RL, Roush GC. Correlation of clinical and histopathologic features in clinically atypical melanocytic nevi. *Cancer*. 1991;67(12):3157-3164.
9. Kelly JW, Crutcher WA, Sagebiel RW. Clinical diagnosis of dysplastic melanocytic nevi. *J Am Acad Dermatol*. 1986;14(6):1044-1052.
10. Friedman RJ, Heilman ER, Rigel DS, Kopf AW. The dysplastic nevus: clinical and pathologic features. *Dermatol Clin*. 1985;3(2):239-249.
11. Clemente C, Cochran AJ, Elder DE, et al. Histopathologic diagnosis of dysplastic nevi: concordance among pathologists convened by the World Health Organization Melanoma Programme. *Hum Pathol*. 1991;22(4):313-319.
12. Elder DE. Dysplastic naevi: an update. *Histopathology*. 2010;56(1):112-120.
13. Roush GC, Nordlund JJ, Forget B, et al. Independence of dysplastic nevi from total nevi in determining risk for nonfamilial melanoma. *Prev Med*. 1988;17(3):273-279.
14. Halpern AC, Guerry D 4th, Elder DE, et al. Dysplastic nevi as risk markers of sporadic (nonfamilial) melanoma. A case-control study. *Arch Dermatol*. 1991;127(7):995-999.
15. Kraemer KH, Greene MH, Tarone R, Elder DE, Clark WH Jr, Guerry D 4th. Dysplastic nevi and cutaneous melanoma risk. *Lancet*. 1983;2(8358):1076-1077.
16. Nordlund JJ, Kirkwood J, Forget BM, et al. Demographic study of clinically atypical (dysplastic) nevi in patients with melanoma and comparison subjects. *Cancer Res*. 1985;45(4):1855-1861.
17. MacKie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. *Lancet*. 1989;2(8661):487-490.
18. Holly EA, Kelly JW, Shpall SN, Chiu SH. Number of melanocytic nevi as a major risk factor for malignant melanoma. *J Am Acad Dermatol*. 1987;17(3):459-468.
19. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I. common and atypical naevi. *Eur J Cancer*. 2005;41(1):28-44.
20. Piepkorn M, Meyer LJ, Goldgar D, et al. The dysplastic melanocytic nevus: a prevalent lesion that correlates poorly

with clinical phenotype. *J Am Acad Dermatol*. 1989;20(3):407-415.
21. Pozo L, Naase M, Cerio R, Blanes A, Diaz-Cano SJ. Critical analysis of histologic criteria for grading atypical (dysplastic) melanocytic nevi. *Am J Clin Pathol*. 2001;115(2):194-204.
22. Duncan LM, Berwick M, Bruijn JA, Byers HR, Mihm MC, Barnhill RL. Histopathologic recognition and grading of dysplastic melanocytic nevi: an interobserver agreement study. *J Invest Dermatol*. 1993;100(3):318S-321S.
23. Elmore JG, Barnhill RL, Elder DE, et al. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study. *BMJ*. 2017;357:j2813.
24. Nelson KC, Grossman D, Kim CC, et al. Management strategies of academic pigmented lesion clinic directors in the United States. *J Am Acad Dermatol*. 2018;79(2):367-369.
25. Strazzula L, Vedak P, Hoang MP, Sober A, Tsao H, Kroshinsky D. The utility of re-excising mildly and moderately dysplastic nevi: a retrospective analysis. *J Am Acad Dermatol*. 2014;71(6):1071-1076.
26. Engeln K, Peters K, Ho J, et al. Dysplastic nevi with severe atypia: long-term outcomes in patients with and without re-excision. *J Am Acad Dermatol*. 2017;76(2):244-249.
27. Marghoob AA, Changchien L, DeFazio J, et al. The most common challenges in melanoma diagnosis and how to avoid them. *Australas J Dermatol*. 2009;50(1):1-13.
28. Nardone B, Martini M, Busam K, Marghoob A, West DP, Gerami P. Integrating clinical/dermatoscopic findings and fluorescence in situ hybridization in diagnosing melanocytic neoplasms with less than definitive histopathologic features. *J Am Acad Dermatol*. 2012;66(6):917-922.
29. Duffy KL, Mann DJ, Petronic-Rosic V, Shea CR. Clinical decision making based on histopathologic grading and margin status of dysplastic nevi. *Arch Dermatol*. 2012;148(2):259-260.
30. Stevenson AD, Mickan S, Mallett S. Systematic review of diagnostic accuracy of reflectance confocal microscopy for melanoma diagnosis in patients with clinically equivocal skin lesions. *Dermatol Pract Concept*. 2013;3(4):19-27.
31. Pellacani G, Longo C, Malvehy J, et al. In vivo confocal microscopic and histopathologic correlations of dermoscopic features in 202 melanocytic lesions. *Arch Dermatol*. 2008;144:1597-1608.
32. Piepkorn MW, Barnhill RL, Elder DE, et al. The MPATH-Dx reporting schema for melanocytic proliferations and melanoma. *J Am Acad Dermatol*. 2014;70(1):131-141.
33. Lott JP, Elmore JG, Zhao GA, et al. Evaluation of the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) classification scheme for diagnosis of cutaneous melanocytic neoplasms: results from the International Melanoma Pathology Study Group. *J Am Acad Dermatol*. 2016;75(2):356-363.
34. Braun RP, Gutkowicz-Krusin D, Rabinovitz H, et al. Agreement of dermatopathologists in the evaluation of clinically difficult melanocytic lesions: how golden is the 'gold standard'? *Dermatology*. 2012;224(1):51-58.
35. Sachdeva M, Frambach GE, Crowson AN, Deng AC, Mihm MC Jr, Magro CM. De novo intraepidermal epithelioid melanocytic dysplasia as a marker of the atypical mole phenotype — a clinical and pathological study of 75 patients. *J Cutan Pathol*. 2005;32(9):622-628.
36. Ferrara G, Argenyi Z, Argenziano G, et al. The influence of clinical information in the histopathologic diagnosis of melanocytic skin neoplasms. *PLoS One*. 2009;4(4):e5375.
37. Longo C, Piana S, Lallas A, et al. Routine clinical-pathologic correlation of pigmented skin tumors can influence patient management. *PLoS One*. 2015;10(9):e0136031.
38. Shahriari N, Grant-Kels JM, Rabinovitz H, Oliviero M, Scope A. Reflectance confocal microscopy may enhance the accuracy of histopathologic diagnosis: a case series. *J Cutan Pathol*. 2019;46(11):830-838.
39. Pellacani G, Farnetani F, Gonzales S, et al. In vivo confocal microscopy for detection and grading of dysplastic nevi: a pilot study. *J Am Acad Dermatol*. 2012;66(3):e109-e121.
40. Borsari S, Pampena R, Benati E, et al. In vivo dermoscopic and confocal microscopy multistep algorithm to detect in situ melanomas. *Br J Dermatol*. 2018;179(1):163-172.
41. Segura S, Puig S, Carrera C, Palou J, Malvehy J. Development of a two-step method for the diagnosis of melanoma by reflectance confocal microscopy. *J Am Acad Dermatol*. 2009;61(2):216-229.