Published in final edited form as:

Dermatol Clin. 2016 October ; 34(4): 395–409. doi:10.1016/j.det.2016.05.003.

Discriminating Nevi from Melanomas: Clues and Pitfalls

Cristina Carrera, MD, PhD^a and Ashfaq A. Marghoob, MD^{b,*}

^aMelanoma Unit, Department of Dermatology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, CIBER de Enfermedades Raras, Instituto de Salud Carlos III, University of Barcelona, Villarroel 170, Escala 1-4, Barcelona 08036, Spain

^bDermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 800 Veterans Memorial Highway, 2nd Floor, Hauppauge, NY 11788, USA

Keywords

Atypical nevi; Confocal; Diagnostic accuracy; Differential diagnosis; Early detection; Nevus; Melanoma

INTRODUCTION

Challenges in Early Detection of Melanoma

Despite great advances made in the treatment of late-stage melanoma, the best chance of survival hinges on early detection.^{1,2} However, detection pressure leading to a heightened sensitivity for finding thinner and smaller melanomas is usually coupled to a lowering of specificity, which results in the biopsy of many nevi. Ideally, surveillance of high-risk patients for melanoma via total-body skin examination aided by technology (eg, dermoscopy, reflectance confocal microscopy [RCM]) should aim to maintain a high sensitivity for the detection of melanoma while at the same time prevent the excision of as many nevi as possible.³ Parameters that can be used to track surveillance efficiency is monitoring ones benign to malignant biopsy ratio (B:M ratio), ratio of thick to thin melanomas, and mean/median melanoma thickness. Total-body photography was one of the first technologies introduced aimed at improving the sensitivity and specificity for melanoma detection. It has been shown that total-body photographs lead to the detection of thinner melanomas and less biopsies of benign nevi with a B:M ratio of 17:1 compared with 45:1 when the examination is performed without photographs.⁴ Dermoscopy has also been shown to lead to the diagnosis of thinner melanomas.⁵ Dermoscopy and digital monitoring has further improved the B:M ratio to between 4 to 7:1^{6–10} and RCM has continued to improved this ratio to about 2:1.^{11–14} RCM has demonstrated an improvement in the diagnostic accuracy of physicians for melanoma detection with a mean sensitivity of 93% and specificity of 76%.¹⁵

*Corresponding author. marghooa@mskcc.org.

No conflict of interests.

Of course, although RCM can greatly impact diagnostic accuracy, it does require learning the features associated with melanoma and nevi. The first section of this article reviews the common clinical scenarios in which RCM can enhance the detection of early melanoma. The second part focuses on the main RCM features used to differentiate nevi from melanoma. Lastly, the RCM pitfalls, including the false-positive nevi and false-negative melanomas, are discussed.

ROLE OF REFLECTANCE CONFOCAL MICROSCOPY IN DETECTING MELANOMA: CLINICAL APPLICATIONS

Patients with the Atypical Mole Syndrome

Numerous studies have shown that individuals with many nevi and individuals with large acquired nevi (>5 mm in diameter) are at increased risk for developing melanoma. The presence of many nevi displaying increased variability of size, shape, and color allows easy identification of this high-risk population. Although melanoma may develop in association with any nevus, most melanomas develop de novo; thus, prophylactic excision of nevi is an inefficient strategy to prevent melanoma.¹⁶ The methods used to find melanoma within a sea of many nevi relies on finding outlier lesions (the ugly duckling sign)^{17,18} and in identifying lesions that are new or have changed over time. Although change is a highly sensitive criterion for melanoma detection, it lacks specificity. Less than 10% of changing lesions identified during digital total-body photography and digital sequential dermoscopy prove to be melanoma.^{8,19} Several studies have demonstrated that focal dermoscopic structural changes are significantly associated with melanoma, however; it remains extremely difficult to differentiate changing atypical nevi from early melanoma via dermoscopy.²⁰

Approximately 8% to 10% of lesions monitored with dermoscopy, total-body photography, and sequential digital dermoscopy end up getting biopsied.⁸ If RCM is added as another investigative layer, approximately 70% of the excisions of changing or equivocal nevi could potentially be avoided without decreasing the sensitivity for melanoma detection.^{20,21} Table 1 summarizes the RCM features used to help differentiate melanoma from nevi. The main RCM features associated with melanoma include the presence of roundish pagetoid cells, atypical cells at the basal layer, non-edged papilla, and nucleated atypical cells within the dermis. Based on the aforementioned features, 2 algorithms have been published that are designed to help diagnose melanoma via RCM with high sensitivity and specificity^{11,12} (Figs. 1 and 2). In addition, another algorithm was created (Fig. 3) to assist in characterizing the degree of atypia present within melanocytic lesions.²² The combination of dermoscopy, digital follow-up, and RCM in the evaluation of equivocal melanocytic lesions has dramatically reduced the number of excisions of benign lesions in patients with the atypical mole syndrome while at the same time improved our ability to detect subtle melanomas.²³ Figs. 4 and 5 showcase 2 lesions for which dermoscopy was unable to correctly diagnose the lesion as melanoma or dysplastic nevus; however, RCM was able to make the correct diagnosis.

Patients Receiving BRAF Inhibitors for BRAF Mutant-Metastatic Melanoma

It is well documented that nevi in patients receiving BRAF inhibitors frequently undergo changes. These patients are also at increased risk for developing new primary BRAF wild-type melanomas.^{24–26} Although the natural biology of nevi changing under the influence of a BRAF inhibition remains unclear, many of these changing nevi have clinical, dermoscopic, RCM, and histopathology morphologic features that overlap with melanoma. Thus, any changing nevus that has RCM features suggestive of malignancy should be excised.^{24,26}

Other Patients at High Risk for Melanoma

Carriers of mutations in high-susceptibility melanoma genes, such as *CDKN2A*, *BAP1*, *POT1*,²⁷ as well as patients with xeroderma pigmentosum,²⁸ albinism, red-hair *MC1R* polymorphisms, or immunosuppressed patients (eg, transplant recipients) may all benefit from surveillance to help find early curable melanoma using all of the aforementioned tools, including RCM.

Dermoscopically Feature-Poor and Amelanotic Tumors

Lesions that reveal nonspecific or few to no dermoscopic structures are known as featureless or structureless lesions. These dermoscopic feature-poor lesions pose a challenge because melanomas as well as benign lesions can present in this manner. Before availability of RCM, the management of these lesions was to biopsy them or to subject them to digital monitoring and resort to biopsy if changes developed. RCM has facilitated our ability to correctly diagnose many of these dermoscopic feature poor. A recent retrospective study demonstrated that among 130 featureless lesions,²⁹ all the melanomas (n = 6 cases) were correctly diagnosed based on the presence of many roundish pagetoid cells (5 or more per square millimeter) and/or by marked disarrangement of the junctional architecture. In contrast, only 17.7% (n = 30) of nevi were incorrectly diagnosed as melanoma (false positive).³⁰ In addition, RCM was also found to be helpful in evaluating small-diameter (ie, incipient melanomas) melanomas.³¹ With RCM, the combination of cytologic atypia with cellular pleomorphism and architectural disorder with irregular clods was found to be strong criteria for the identification of incipient melanomas. Each of the following 3 RCM features were found to be independently associated with small melanomas: the presence of at least 5 pagetoid cells per square millimeter, dendrites or tangled lines (meaning short fine lines with no visible nucleus interlacing the keratinocytes) within the epidermis, and atypical roundish cells at the dermoepidermal junction (DEJ) (see Fig. 4).

Amelanotic melanomas are by definition feature-poor lesions. However, because melanocytes, including melanocytes in amelanotic tumors, contain highly refractile melanosomes, RCM has proven to be an ideal instrument for analyzing these lesions. RCM enables the visualization of architectural and cytologic structures in melanocytic tumors, including tumors lacking pigment on dermoscopy (Fig. 6). It has been shown that RCM improves the ability to correctly identify both nevi and early melanomas in red-haired and fair skin-type patients, such as those with albinism.^{32–34}

Collision Tumors

Collision tumors can be difficult to diagnose based on dermoscopy findings. This difficulty is especially true for collision tumors composed of a malignancy arising in association with a benign lesion. In one study, RCM was able to identify the malignant component in 19 out of 20 collision tumors.³⁵

REFLECTANCE CONFOCAL MICROSCOPY FEATURES USED TO DIFFERENTIATE NEVI FROM MELANOMA

Histopathologic-proven benign nevi that are dermoscopically equivocal or atypical (ie, false positive for melanoma on dermoscopy) are usually easy to differentiate from melanoma by RCM. Melanoma can be ruled out if the lesion displays typical RCM features encountered in nevi while at the same time lacking the features associated with melanoma. The following 5 scenarios are most commonly encountered in routine practice. In all 5 cases the nevi are found to be clinically or dermoscopically equivocal, but RCM reveals a benign pattern.

- a. Dermoscopy reveals an atypical or irregular pigment pattern (eg, atypical network, irregular globules, eccentric asymmetric dermoscopic islands with darker pigment; RCM shows a well-circumscribed nevus with edged papilla and a clod, ringed or meshwork pattern).³⁶
- b. Dermoscopy reveals a hyperpigmented structureless pattern (black lamella and/or black-blue area), and RCM shows a regular cobblestone pattern of the epidermis and/or a dense infiltration of melanophages appearing as bright plump cells in the superficial dermis. The cobblestone pattern corresponds to melanized keratinocytes situated in the basal and spinous layers of the skin.
- c. Dermoscopy of a pink macule reveals a nonspecific vascular pattern; RCM demonstrates one of the aforementioned benign nevus patterns or a Spitz nevus pattern consisting of regular dense uniform clods occupying the entire epidermis, DEJ, and superficial dermis.³⁷
- d. Many melanomas found because of changes noted on sequential digital dermoscopy are dermoscopically featureless lesions and, based on primary morphology alone, are not distinguishable from nevi. It has also been shown that less than 20% of changing lesions found on sequential digital dermoscopy prove to be melanoma.⁸ However, as discussed previously, these dermoscopically featureless melanomas can usually be correctly diagnosed with RCM. And according to recent publications, approximately 70% of the changing nevi reveal one of the benign RCM nevus patterns mentioned previously^{20,21,34} (see Fig. 5).
- e. Recurrent pigmentation in a scar of a previously biopsied presumed nevus can be disconcerting. In most cases the repigmentation is due to benign reactive pigmentation or due to persistence of an incompletely excised nevus. However, on rare occasions, the recurrent pigmentation may represent melanoma. RCM can assist in evaluating these lesions. In the absence of atypical RCM features,

such as pagetoid infiltration of the epidermis or atypical nucleated cells at the DEJ, the likelihood of melanoma becomes exceeding remote.³⁸

CHALLENGING LESIONS ON REFLECTANCE CONFOCAL MICROSCOPY: PITFALLS OF REFLECTANCE CONFOCAL MICROSCOPY

Unfortunately, diagnostic accuracy by RCM is not 100% and therefore it is necessary to acknowledge some limitations of the technique and to interpret the findings in context with the entire clinical scenario (Box 1).

False-Negative Melanomas

False-negative melanomas are those that manifest a morphology resembling a benign lesion. Recently it was estimated that less than 4% of melanomas fail to be detected with RCM alone; however, just one case out of 201 would have failed detection if the RCM findings were seen in context with the clinical and/or dermoscopic examination. Thus, placing RCM findings in context with patient-related information and clinical history will help avoid missing most of these melanomas.³⁹

Nodular/dermal/desmoplastic melanoma

Melanomas in which the diagnostic pathology features are located below the papillary dermis cannot be diagnosed with RCM because the imaging of RCM is unable to penetrate past the depth of approximately 150 to 200 μm . Pure nodular melanomas⁴⁰ often reveal a thin and well-conserved epidermis with a normal honeycombed pattern with fewer atypical features, such as pagetoid cells in the suprabasal layer. In such cases, the RCM findings can mistakenly lead to a benign diagnosis. In some cases, RCM may only reveal inflammation and a disarranged architectural pattern that may lead to an incorrect diagnosis of an irritated nevus. However, a retrospective study by Longo and colleagues⁴¹ evaluated 140 nodular lesions (including 23 pure nodular melanomas) and they found that approximately 86% of nodular lesions that were not ulcerated or hyperkeratotic were correctly diagnosed via RCM examination. Remarkably, RCM reached 96.5% sensitivity and 94.1% specificity for the diagnosis of melanoma despite the fact that all lesions were nodular palpable lesions.⁴¹ In nodular melanoma, one may observe a disarranged DEJ, nonedged papillae, and/or cerebriform nests in the superficial dermis. It should be noted that the presence of cerebriform nests on RCM is highly specific for nodular areas of invasive melanoma.

Nevoid melanoma

Melanomas composed cytologically of mostly small-melanocytes forming nests are diagnostically challenging not only by RCM but also by histopathology.

Verrucous melanoma

RCM of lesions, including melanomas, that are heavily pigmented and associated with hyperkeratosis or ulceration are challenging. This challenge stems from the fact that, in hyperkeratotic lesions, the RCM light penetration often does not reach to a sufficient depth

to allow clear visualization of DEJ. However, a few cases have been reported whereby RCM allowed for the observation of melanocytic proliferation at the DEJ.⁴²

Early melanomas arising in melanocytic nevi—The RCM pitfall here stems from the fact that the malignant findings may be located focally and, therefore, get missed on RCM imaging within the background context of an otherwise typical RCM melanocytic nevus morphology. To avoid this pitfall requires complete and meticulous examination of the entire lesion via RCM, which can be a time-consuming endeavor.⁴³

False-Positive Melanomas

False-positive melanomas are nevi that display RCM morphologic features suggestive of melanoma.

Spitz nevi or heavily pigmented fusiform cellular nevi (Reed nevi)

Although the presence of pagetoid spread of melanocytes within the epidermis is an important clue for melanoma diagnosis, this feature is also observable in Spitz nevi. In Spitz nevi the pagetoid cells are usually sporadically distributed in the suprabasal layers and clustered toward the center of the lesion, whereas in melanoma these cells are randomly distributed in a more diffuse manner. However, in the face of an RCM image displaying pagetoid cells, it is often impossible to differentiate Spitz tumors from melanoma. Spitz nevi can also be an RCM pitfall because, similar to melanoma, they can manifest architectural disarray and cytologic atypia.^{44,45} Of course, the depth of penetration of RCM imaging precludes any ability to evaluate the presence of cell maturation in the deeper dermis, which is an important feature of these nevi. Although Spitz nevi can have pagetoid cells, Spitz nevi often display a normal honeycombed pattern on RCM. The globular Spitz nevi present with elongated clods and clusters at the DEJ. These clusters tend to be of uniform size and shape with a tendency toward confluence. They also have a characteristic abrupt border with refractive polygonal aggregates or clods at the lesion's perimeter. In the case of heavily pigmented melanocytic lesions displaying a blue color, RCM enables the distinction between blue veil due to regression and blue veil due to melanocytosis. The former is characterized by plump bright cells on RCM, which corresponds to melanophages and inflammatory infiltrate in the papillary dermis on histology. The latter is characterized by the presence of epidermal and dermal features consistent with diagnosis of melanoma and includes the following features: disarranged pattern, pagetoid cells, cytologic and architectural atypia, nonhomogeneous and cerebriform clusters, and dermal nucleated cells (Fig. 7).

Nevi with pagetoid infiltration of single cells

RCM enables excellent visualization of melanocytes spreading upward in a pagetoid fashion. The problem is that the simple presence of pagetoid cells does not make a diagnosis of melanoma. For example, pagetoid cells can be seen in Spitz nevi and nevi of special sites such as those on the breast and genital region. Pathologists interpret the significance of pagetoid spread by evaluating the degree of spread within the context of the rest of the lesion when differentiating nevi from melanoma. However, because the entire cellular details, including evaluating cellular maturation as a function of depth, cannot be assessed

adequately with RCM, the visualization of pagetoid infiltration on RCM in a nevus usually leads to a false-positive diagnosis of melanoma. Although it has been suggested that the presence of a disarranged pattern in the superficial layers together with numerous large and closely arranged cells extending into the stratum corneum correlates strongly with malignancy, melanoma cannot be excluded simply based on the absence or paucity of pagetoid cells on RCM imaging because at least 10% of melanomas will have no or only a few such cells.⁴⁶

Inflamed or irritated nevi

RCM imaging of inflamed nevi including halo nevi and nevi with eczematouslike inflammation (Meyerson nevus) reveal architectural disarray at the DEJ, bright particles, and plump bright cells (corresponding to melanophages) in the dermal papillae. In addition, these nevi can also show roundish and dendritic pagetoid cells on RCM imaging. Although the dendritic cells noted in these inflamed nevi correspond to intraepidermal melanocytes, more often than not they correspond to Langerhans cells (presented by Martins da Silva V et al. at the 73rd American Academy of Dermatology [AAD] meeting, San Francisco, unpublished data, 2015). Currently it is impossible to differentiate, with certainty, dendritic melanocytes from Langerhans cells via RCM imaging.⁴⁷

Nevi after ultraviolet radiation exposure

It has been demonstrated that acute and repeated UV radiation (UVR) exposure to nevi can lead to transient melanomalike findings on dermoscopy, RCM, and even histopathology. Several studies have demonstrated melanocytic activation and cell proliferation in nevi after a single dose of UV-B.^{48,49} Inflammation-induced changes and melanocytic activation can in fact be observed in vivo, with RCM revealing the presence of intraepidermal dendritic cells and bright particles at DEJ and papillary dermis. If RCM features were evaluated in isolation and without knowledge that the nevus was recently irradiated by UVR, the RCM features would lead to the false diagnosis of melanoma (presented by Takigami MC et al. at the 73rd American Academy, San Francisco, unpublished data, 2015).

SUMMARY

Accurate and thorough RCM evaluation of clinically and dermoscopically equivocal melanocytic lesions allows for improved differentiating of melanoma from nevi. It leads to the recognition of incipient melanomas while at the same time decreasing the unnecessary excision of many nevi. However, although RCM has significantly improved our sensitivity and specificity and impacted our B:M ratio in a positive manner, it is not 100% accurate. The situations responsible for a false-positive diagnosis of melanoma and perhaps more importantly the situations resulting in a false-negative diagnosis of melanoma are important to acknowledge. Obviously, it is imperative that the RCM operator also understands the limitations of RCM, such as its inability to view the deeper component of lesions. As a general rule, correlation should always be sought between the clinical, dermoscopic, and RCM findings for all lesions. This correlation will help minimize the risk of missing melanomas. In other words, RCM should be viewed as a complementary tool that needs to be integrated with other diagnostic data. Although all this information may create noise, the

experienced clinician will be able see the signal to help him or her arrive at the correct management decision via abductive reasoning. For example, in the case of flat lesions with significant clinical-dermoscopic concern but with benign features on RCM imaging, short-term digital monitoring would be an acceptable alternative to immediate biopsy. In contrast, suspicious nodular lesions should be biopsied even if no concerning features are seen on RCM imaging.⁵⁰

It should be intuitively obvious that training and experience with RCM image acquisition, RCM image interpretation, and dermatopathology will improve the operator's diagnostic acumen.

Acknowledgments

Funding Sources: The research at the Melanoma Unit in Barcelona is partially funded by: Spanish Fondo de Investigaciones Sanitarias grants 09/01393 and 12/00840; CIBER de Enfermedades Raras of the Instituto de Salud Carlos III, Spain; AGAUR 2009 SGR 1337 and AGAUR 2014_SGR_603 of the Catalan Government, Spain; European Commission under the 6th Framework Programme, Contract No. LSHC-CT-2006-018702 (GenoMEL) and by the European Commission under the 7th Framework Programme, Diagnostocs (CE_CIP-ICT-PSR-13-7); The National Cancer Institute (NCI) of the US National Institute of Health (NIH) (CA83115) and a grant from "Fundació La Marató de TV3, 201331-30", Catalonia, Spain.

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Box 1**Pitfalls in reflectance confocal microscopy****Possible false-positive melanoma by RCM**

1. Atypical nevi with a high degree of atypia
2. Nevi with focal pagetoid cells infiltrating the epidermis as can occur in nevi of special sites or in acral or mucosal nevi; can also be seen in inflamed nevi, such as halo nevi
3. Spitz nevi or spitzoid lesions
4. Nevi after acute UV light exposure

Possible false-negative melanomas by RCM

1. There is a nodular, dermal, or desmoplastic melanoma. Deep component of melanomas cannot be assessed via RCM because of limitations in the depth of RCM light penetration, which is about 200 μm .
2. Nevoid melanoma may only have focal pagetoid infiltration and may consist of small monomorphic melanoma cells, which can resemble the cells seen in nevi.
3. Focal melanoma arising in a nevus. The focal melanoma features may get overlooked in an otherwise benign appearing RCM background revealing features of the nevus.
4. Verrucous melanomas or seborrheic keratosis-like melanomas with heavily pigmented epidermis.

KEY POINTS

- The improved ability to differentiate nevi from melanoma via reflectance confocal microscopy (RCM) has the potential to greatly impact the management of patients with multiple atypical nevi, changing nevi, and hypomelanotic or amelanotic lesions.
- Clinically subtle melanomas usually reveal architectural disarray of the dermoepidermal junction (DEJ) with nonedged papillae and atypical nucleated cells along the basal layer; in addition, the presence of pagetoid cells consisting of large roundish and/or dendritic refractile cells is a prominent feature seen in many melanomas.
- Most nevi manifest edged papillae with a combination of benign patterns at DEJ (ie, clod pattern, ringed pattern, meshwork pattern). Mild focal architectural disarray may also be seen.
- False-positive cases of melanoma on RCM are often encountered when evaluating nevi that prove on histology to have a high degree of dysplasia, a spitzoid morphology, or are inflamed.
- False-negative cases of melanoma often reveal minimal architectural disarray on RCM. Although they tend to lack pagetoid cells, they also do not display any of the benign RCM nevus patterns.

Fig. 1.

The Barcelona algorithm¹² is a 2-step process. The first step requires the clinician to differentiate melanocytic from nonmelanocytic tumors. A melanocytic lesion should be suspected if the dermal papillae are visualized and at least one of the following features is also seen: cobblestone pattern, pagetoid cells, and/or refractile nests. Lesions not displaying any of the aforementioned features are then evaluated to determine if they have any RCM features diagnostic of basal cell carcinoma, seborrheic keratosis, angioma, or dermatofibroma. If not, then by default the lesion is considered to be a melanocytic tumor.

The second step of the *Barcelona algorithm helps to differentiate melanoma from nevus*. Lesions that are dermoscopically suspicious for melanoma are evaluated via RCM for the presence of 2 risk features (+1 point) and 2 protective features (−1 point) for melanoma diagnosis. The high-risk criteria include (A) pagetoid roundish cells in the superficial epidermal layers (*yellow arrows*) and (B) atypical nucleated cells in the papillary dermis (*yellow arrows*). The protective criteria include (C) presence of typical basal cells (*squares*) and (D) presence of edged papillae (*asterisks*) at the dermoepidermal junction. The points for the presence of any of the 4 features are summed together, and the final score is used to predict the probability of melanoma. Lesions with a score of −1 or greater have a sensitivity of 100% and specificity of 57.1% for melanoma. Lesions with scores of 0 or greater have a high probability of being melanoma with a sensitivity of 86.1% and specificity of 95.3%.

MAJOR CRITERIA Modena Algorithm (Melanoma ≥ 3)

Fig. 2.

Modena algorithm¹¹ classifies lesions into melanoma or nevus based on the presence of 2 main risk features (+2 points for the presence of each, for a maximum of 4 points) observed at dermoepidermal (DE) junction: (1) cellular atypia at basal layer (A, *squares*); (2) nonedged papillae (B, *asterisks*). In addition, the lesion is evaluated for the presence of 4 minor risk features (+1 point for the presence of each, for a maximum of 4 points): (1) widespread pagetoid infiltration of spinous layer (C, *squares*); (2) roundish pagetoid cells (D, *arrows*); (3) cerebriform nests in dermis (E, *squares*); (4) nucleated atypical cells in

upper dermis (F, arrows). Lesions with a total score of 3 or greater should be excised to rule out melanoma (sensitivity 91.9%, specificity 69.3%).

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Fig. 3.

Algorithm to distinguish dysplastic nevi from melanoma as described by Pellacani and colleagues.²² First step requires evaluation of the lesion for the presence or absence of cytologic and architectural atypia; junctional nests of different size or with sparse cells of differing refractility (nonhomogeneous) are considered irregular. Junctional thickenings or short interconnections are irregular refractile aggregates between papillae. Absence of atypical cells in epidermis and atypical junctional nests or aggregates is suggestive of a benign nondysplastic nevus. The second step quantifies the degree of atypia and allows differentiation of probable dysplastic nevi from melanoma. The presence of widespread pagetoid infiltration encompassing at least 50% of lesion, diffuse cytologic atypia at the dermoepidermal junction (DEJ) involving at least 50% of lesion, or nonedged papillae encompassing at least 10% of the lesion is suggestive of melanoma.

Fig. 4.

(A) Dermoscopy of a 3.0×3.5 -mm new pigmented lesion noted on the forearm of a patient with a history of multiple primary melanomas. The lesion has a globular pattern with an irregular arrangement of globules at the periphery. (B) A 5×5 -mm RCM mosaic at the dermoepidermal junction (DEJ) layer shows a well-demarcated lesion that is predominantly composed of a clod pattern at the periphery (*arrows*). A few small irregular nonaggregated clusters are visible (*red square*) and isolated eccentric pagetoid cells can also be seen (*yellow square*). (C) Single RCM image shows large atypical roundish and dendritic pagetoid cells (*arrows*). (D) Single RCM image shows pagetoid cells (*asterisks*) and a red arrow pointing to a cluster.

within the superficial epidermis (*yellow arrows*). (*D*) Single RCM image at DEJ displaying nonedged papillae (*asterisks*) and junctional thickenings (*red arrow*) with dendritic cells along the basal layer. DIAGNOSIS: in situ melanoma.

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Fig. 5.

(A) This patient has a history of multiple primary melanomas. Two changing lesions were detected on his back during digital surveillance. (B) Sequential digital dermoscopy of the 3-mm lesion on the central lumbar area disclosed progressive enlargement of the lesion with development of an atypical network and peripheral blotch. (C, D) RCM mosaics of epidermal layers show a well-conserved cobblestone pattern (*yellow squares*). One single isolated small dendritic cell was visible in the superficial layers (*arrow*). (E) Mosaic at dermoepidermal junction level shows typical architecture composed of edged papillae (*asterisks*) and meshwork pattern with typical basal cells between the dermal papillae. (F) A compound nevus with a lentiginous growth pattern, bridging of rete ridges, and moderate dysplasia (hematoxylin-eosin, original magnification $\times 20$). These features correlate to the meshwork pattern and junctional thickening seen in (E). **DIAGNOSIS:** Compound melanocytic nevus with moderate atypia.

Fig. 6.

(A) This 5-mm hypomelanotic lesion was noted on the abdomen of this patient. (B) Dermoscopy features were nondiagnostic revealing erythema, milky red area, dotted and linear irregular vessels. (C) RCM examination shows pagetoid roundish cells (*arrows*) both in the superficial epidermal layers (C) and at the DEJ (D–F). Atypical roundish and dendritic large cells are seen along the basal layer resulting in disruption of the DEJ, and nonedged papillae can also be seen (F). **DIAGNOSIS:** Superficial spreading melanoma, Breslow 0.5 mm.

Fig. 7.

(A) This patient presented with a rapidly growing and heavily pigmented lesion on the dorsum of her foot. (B) Symmetric dark brown to black lesion with a superficial black network seen with dermoscopy is fairly characteristic of a Reed's nevus. (C) Single RCM image of the superficial epidermis shows a honeycomb pattern with isolated dendritic pagetoid cells. (D) Single RCM image along the spinosum epidermal layer shows the typical cobblestone pattern, which is due to the presence of pigmented keratinocytes. (E) Single RCM image along the DEJ reveals a meshwork pattern with regular and dense aggregates and junctional thickenings and edged papillae. A few refractile non-nucleated cells within the papillae, corresponding to melanophages, can be seen. **DIAGNOSIS:** Pigmented fusiform cellular Spitz nevus (Reed nevus).

Table 1

Confocal features used to differentiate melanoma from nevi

Evaluation Level	Melanoma	Atypical Nevus	Nevus
Epidermis	Marked or complete loss of honeycomb and/or cobblestone patterns	Variably disarranged honeycomb and/or cobblestone patterns	Well-conserved honeycombed pattern and/or
	Widespread pagetoid cells and large atypical bright cells	A few focal isolated atypical cells mostly located towards the center of the lesion Pagetoid spread is absent or very limited in its extent	Regular cobblestone pattern (when keratinocytes are pigmented)
DEJ	Poorly demarcated lesion	Well-circumscribed lesion	Well-circumscribed lesion
	Moderate to severe distortion of DEJ architecture	Mild to severe distortion of DEJ architecture	Well-defined DEJ architecture
	Nonedged papillae (ill-defined dermal papillae)	Focal areas of nonedged papillae and meshwork pattern	Edged papillae (well-defined margins), regular in shape and distribution
	Irregular, elongated, and fused interpapillary crests resulting in junctional thickenings	Irregular, elongated, and fused interpapillary crests resulting in junctional thickenings	Bright basal cells forming cobblestone and ringed pattern
	Moderate to severe cellular atypia at the basal layer	Junctional nests with irregular shape, size, and location Variable atypia with hyper-refractile cells at basal layer	Dense clusters and/or interpapillary processes forming meshwork and/or clod patterns
Dermis	Atypical nucleated cells within dermal papillae	Bright non-nucleated plump cells (melanophages)	Regular dense and/or some sparse cells within the clods or clusters of cells at DEJ and superficial dermis
	Cerebriiform nests	Bright triangle particles (inflammation)	Uniform cellularity within the clods (occasionally bright roundish nucleated uniform cells can be seen in congenital nevi)
	Bright non-nucleated plump cells (melanophages)	Coarse collagen bundles forming networklike structure	Regular vessels in the center of the papilla
	Bright triangle particles (inflammation)		
	Prominent and atypical vessels		
	Coarse collagen bundles forming a gross networklike structure		

Abbreviation: DEJ, dermoepidermal junction.