Discriminating Nevi from Melanomas: Clues and Pitfalls

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KEYWORDS

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

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.

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

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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]

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, nonedged 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.