Dermatology Practical & Conceptual

Limits of Reflectance Confocal Microscopy in Melanoma Diagnosis

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Melanoma poses a significant challenge in clinical practice due to its aggressive behavior and potential for metastasis [1]. Early and accurate diagnosis of melanoma is paramount for improved patient outcomes and reduced mortality rates [2]. Recent advancements in imaging technologies have introduced noninvasive diagnostic tools with the potential to provide real-time, high-resolution imaging of skin lesions at the cellular level [3,4].

Reflectance confocal microscopy (RCM) has emerged as a promising technique for in vivo melanoma diagnosis, enabling visualization of cellular and subcellular structures within the skin without the need for surgical biopsies [5-7]. RCM operates on the principle of capturing and analyzing light backscattered from different skin layers, particularly the epidermis and superficial dermis. By using a low-power laser as the light source and a pinhole to reject out-of-focus light, RCM achieves optical sectioning and outstanding depth resolution. This capability allows RCM to generate high-resolution, en face imaging of the skin, facilitating visualization of melanocytic lesions at the cellular level. Numerous studies have demonstrated the utility of RCM in aiding the diagnosis of melanocytic lesions, including melanoma. Pellacani et al reported that RCM achieved a sensitivity of 91.9% and 69.3% specificity in differentiating melanoma from benign nevi [5]. Additionally, Guitera et al conducted a multicenter study, showing RCM sensitivity of 91.0% in detecting melanoma, further underlining its potential for early-stage diagnosis [8].

A recent randomized controlled trial demonstrated that the use of RCM improves diagnostic accuracy by reducing the number needed to excise (NNE) [9]. This study was conducted in 3 referral centers specialized in pigmented skin lesions, showing that adjunctive RCM was associated with a higher positive predictive value (18.9 versus 33.3), lower

benign to malignant ratio (3.7:1.0 versus 1.8:1.0), and an NNE reduction of 43.4% (5.3 versus 3.0), when compared with standard therapeutic care only [9].

Despite these promising results, the clinical implementation of RCM is not without its challenges. Interestingly, in the above-mentioned study 15 melanomas were initially misdiagnosed under RCM and were only detected after follow-up (mean Breslow thickness 0.5 mm). Operator dependence, limited imaging depth, and the risk of false positives and false negatives are among the limitations that need to be addressed. To gain a comprehensive understanding of these limitations, a critical evaluation of RCM performance is essential.

In this context, we aim to closely analyze two scenarios: the risk of melanoma overdiagnosis and underdiagnosis using RCM. Our goal is to emphasize the importance of a comprehensive evaluation of the clinical, dermoscopic, and confocal findings in reaching a final decision on whether to biopsy a given lesion or not. Understanding these limitations is crucial for refining diagnostic approaches and optimizing melanoma diagnostic pathways, ultimately leading to improved patient outcomes and more effective melanoma management strategies.

Overdiagnosis

Overdiagnosis of melanoma may occur in case of "dysplastic" nevi, spitzoid lesions and halo nevi, and with pigmented actinic keratosis on the head/neck area. In all these cases, the primary confounding feature is the high probability of encountering intraepidermal dendritic cells, which can correspond to both atypical melanocytes and dendritic Langerhans cells under RCM. The presence of both roundish nucleated and dendritic intraepidermal cells is called "pagetoid spread" in RCM. This feature is a potent predictor of melanoma. However, these cells can also be found in benign lesions, thus increasing the likelihood of overdiagnosis [10-12].

Dysplastic Nevi

Dysplastic nevi, also known as atypical nevi, exhibit overlapping clinical and dermoscopic features with melanoma, presenting a diagnostic challenge for clinicians and pathologists. Under RCM, the presence of intraepidermal atypical cells and architectural disarrangement of the rete ridges are the main features for melanoma diagnosis. However, these features can be found also in the so-called atypical or dysplastic nevi, usually to a lesser extent as compared to melanomas. The differentiation of intraepidermal atypical cells in melanoma and dysplastic nevi poses a significant diagnostic challenge, leading to potential misdiagnosis and subsequent inappropriate management decisions (Figures 1-3) [13,14].

Studies have demonstrated that RCM can accurately characterize cellular atypia, nested patterns, and pagetoid spread, aiding in the differentiation between dysplastic nevi

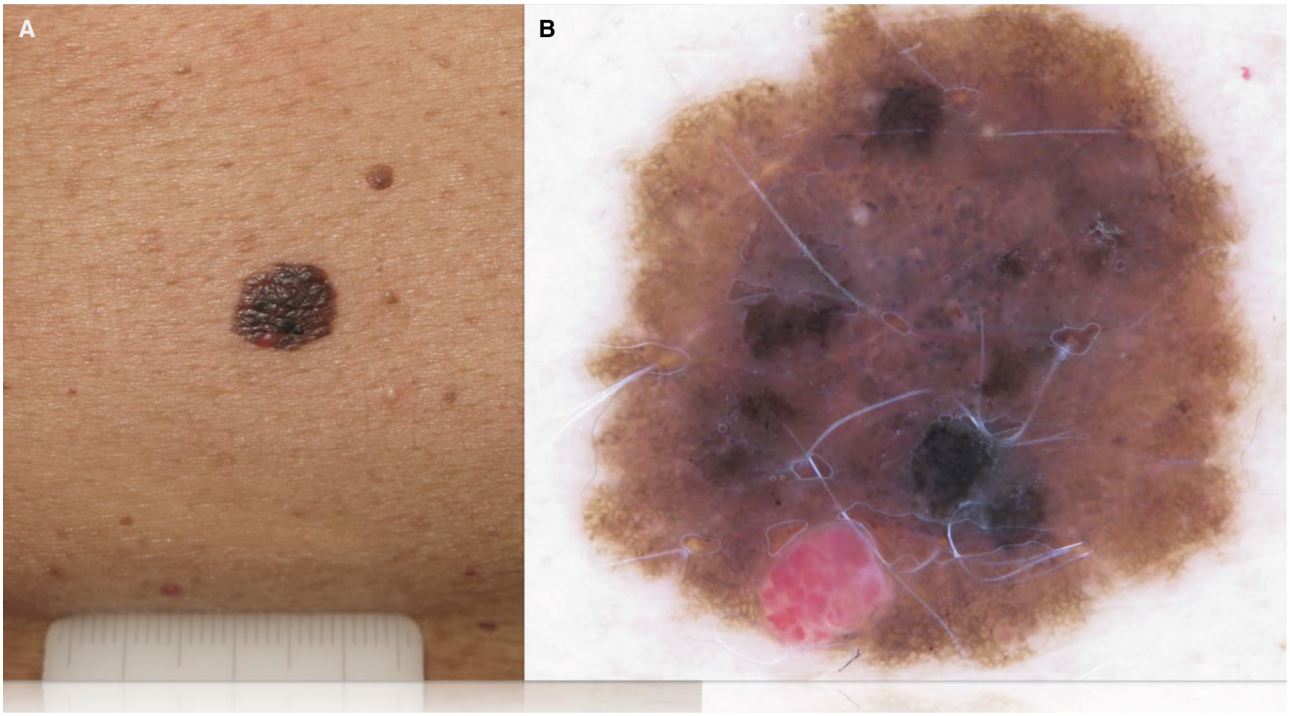

Figure 1. Dysplastic nevus. (A) Clinical appearance of a pigmented macule on the back of a 45-year-old woman. The lesion appears variegated in color, from a light to dark brown coloration, colliding with an angioma. (B) Dermoscopy, showing reticular network in the periphery, irregular hyperpigmented areas in the center, and a colliding angioma.

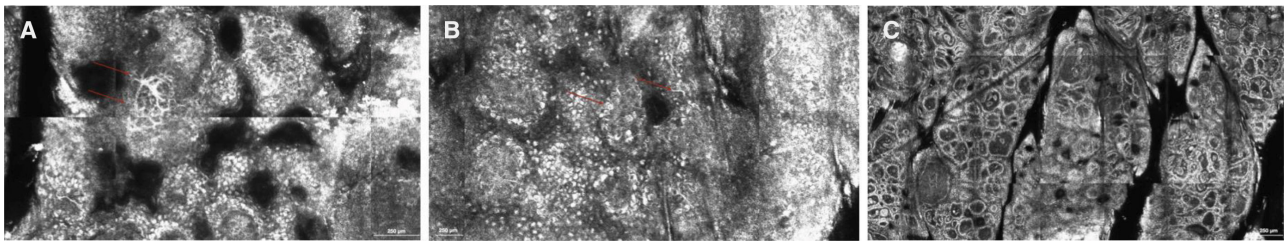

Figure 2. (A) RCM imaging of the case in Figure 1. The epidermis appears hyperkeratotic, with a "geographical" appearance of the epidermal surface. Dendritic cells with long dendrites are visible (red arrows). (B) RCM imaging of the case in Figure 1. RCM image at the level of the spinous layer with multiple roundish pagetoid cells (red arrows). (C) RCM imaging of the case in Figure 1. A ringed and clod pattern is visible at the dermo-epidermal junction. At this level, the architecture of the lesion appears quite regular. However, since there is abundant pagetoid spread present in the superficial layers, the lesion was excised in order to rule out early melanoma.

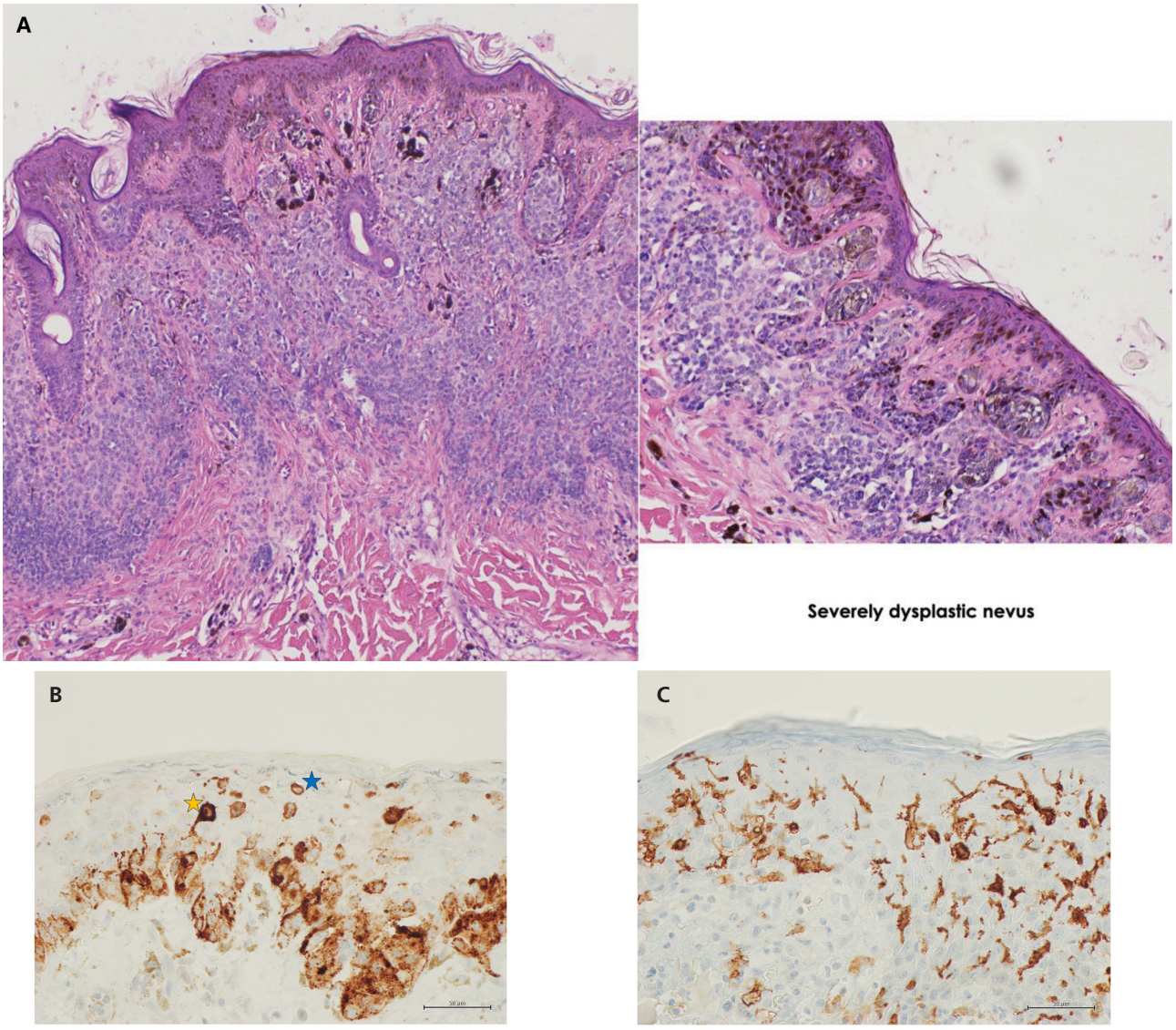

Figure 3. (A) Histological findings in a case of dysplastic nevus. Histological examination shows a compound melanocytic proliferation. The junctional melanocytes are confluent along the elongated rete ridges. The intradermal melanocytes are arranged in nests with evidence of maturation (H&E, original magnification ×100). (B) Histological examination showing pagetoid spread of neoplastic melanocytes in a case of superficial spreading melanoma. Intraepidermal melanocytes showing dendritic (yellow star) or roundish (blue star) shape (HMB45 immunostain, original magnification ×400). (C) Histological examination shows many intraepidermal dendritic cells (Langerhans cells). These cells always have dendritic shape and may simulate intraepidermal melanocytes (CD1a immunostain, original magnification ×400).

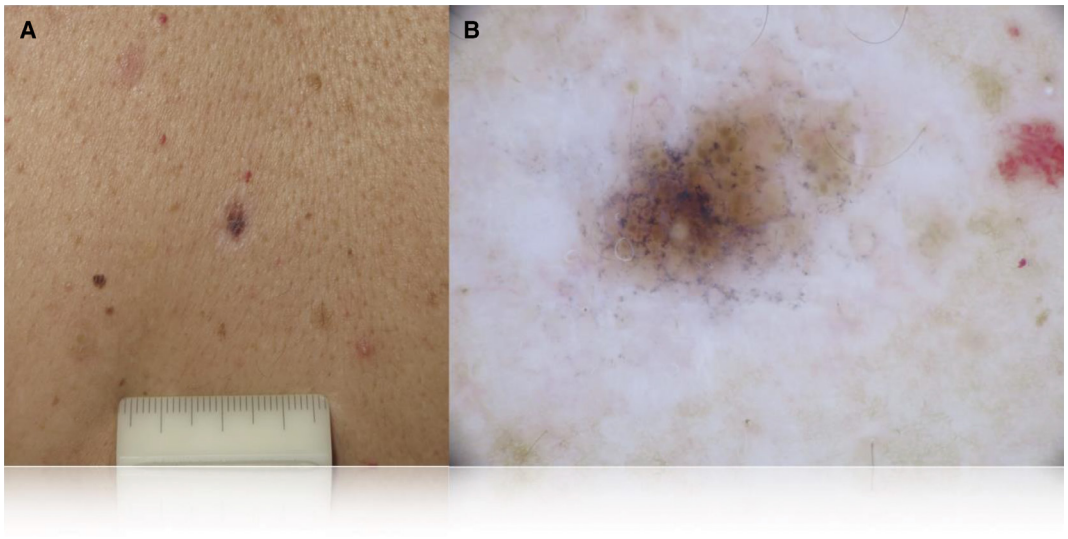

Figure 4. Halo nevus. (A) Clinical image of a pigmented lesion on the back of a 16-year-old boy. A whitish halo surrounding the lesion is visible at careful examination. (B) On dermoscopy, remnants of brownish pigmentation, peppering ,and a white peripheral halo.

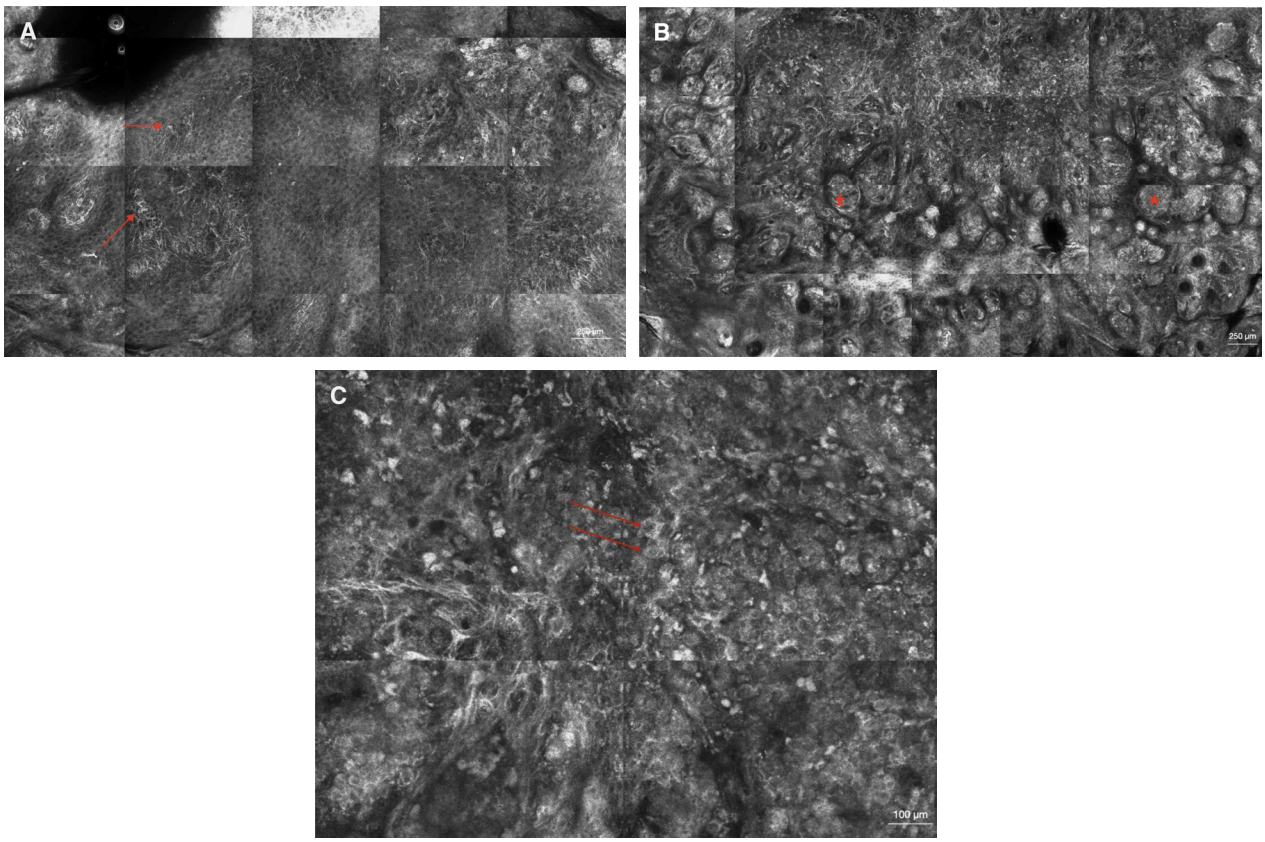

Figure 5. (A) RCM imaging of the case in Figure 4. Numerous roundish and dendritic cells in the epidermis (red arrow). (B) Overall, the lesion appears disarranged with some clods (red star) and a focal loss of structure with numerous dendrites. (C) A close-up of the atypical cells seen in the epidermis (red arrows).

and melanoma [13]. However, in this scenario, the risk of overdiagnosis remains high, and the correct evaluation of these lesions requires a high level of expertise because it relies on a quantitative assessment of the observed atypia. In any event, it is important to highlight that the differential diagnosis of nevi with dysplasia and early melanoma is an ongoing challenge in dermatopathology. A gray zone exists, with a low level of diagnostic agreement among pathologists, and this contributes to the limits of RCM in this field (Figure 1).

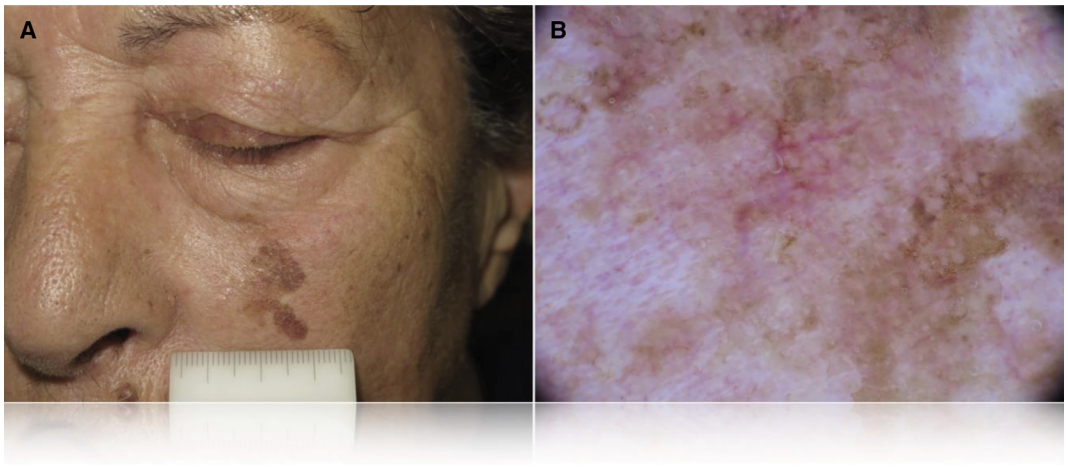

Figure 6. Pigmented actinic keratosis. (A) A flat pigmented macule on the face of a 73-year-old man. (B) On dermoscopy, pseudo-network and gray color around the follicle are visible.

Spitzoid Lesions

The same can happen in Spitz nevi. Several studies attempted to define differentiating features between Spitz nevi and melanoma. A symmetric lesion, well demarcated, with epidermal acanthosis, with a pattern of clods and mainly roundish cells with short dendrites in the epidermis can be most probably diagnosed as Spitz nevus [15]. On the contrary, asymmetry, abundance of atypical intraepidermal cells, and meshwork pattern favor the diagnosis of melanoma. However, as for dermoscopy, differentiating Spitz nevi from melanoma is simply impossible [16]. Management of spitzoid-looking lesions remains based on clinical factors, namely the age of the patient. RCM can be useful in differentiating Spitz nevi from other melanocytic and non-melanocytic lesions such as viral warts, angioma, pyogenic granuloma, and dermatofibroma [17,18].

Halo Nevus

In halo nevi the architectural disarrangement evocates what we can usually observe in melanomas. These lesions can display architectural disorder and plenty of atypical cells at all levels, usually dendritic with very long dendrites. These are most probably Langerhans cells; however, the architectural disarray is usually so high that without clinical and dermoscopic correlation every halo nevus would be excised based on RCM features (Figures 4 and 5) [19].

Pigmented Actinic Keratoses

Pigmented Actinic Keratoses (PAKs) are the main lesions in differential diagnosis with lentigo maligna on the head and neck area. Melanocytes in PAKs are often atypical and they appear once again as roundish to dendritic intraepithelial cells. They are more diffuse than perifollicular; however, this subtle feature is not always obvious when examining the lesions. The surrounding keratinocytes are usually dysplastic, and no signs of melanocytes proliferation is seen at the dermo-epidermal junction (Figures 6 and 7) [20].

Underdiagnosis

The main reason for underdiagnosis in RCM is due to one intrinsic limit of the tool, namely, the limitation in the visualization in depth. When the tumor is deeply located in the dermis one can still observe a normal-appearing epidermis and dermo-epidermal junction, thus leading to incorrect diagnoses. Cases of melanomas resembling dermatofibromas have been described (Figures 8 and 9) [18]. Moreover, acral, hyperkeratotic, and extensively ulcerated lesions are simply not visible under RCM.

A relative limitation is the evaluation of completely amelanotic lesions. These have been previously described as one of the best indications for RCM [21,22]. Amelanotic lesions are frequently misdiagnosed in dermoscopy, and the diagnosis without pigment is one of the main challenging areas for dermoscopists. However, hypomelanotic lesions require a high level of expertise in RCM because the lower contrast due to the absence of melanin can make the differential diagnosis extremely difficult. It is important to evaluate the entire lesion and look carefully for the suspicious features.

Finally, atypical lentiginous proliferations can present only very subtle features under RCM. When examining lentiginous melanoma, a perfectly symmetric ringed pattern can be observed in many cases at the dermo-epidermal junction [23]. Only the experienced eye can distinguish normal-appearing roundish keratinocytes from the atypical roundish, slightly bigger melanocytes present in the epidermis or at the junction in these lesions.

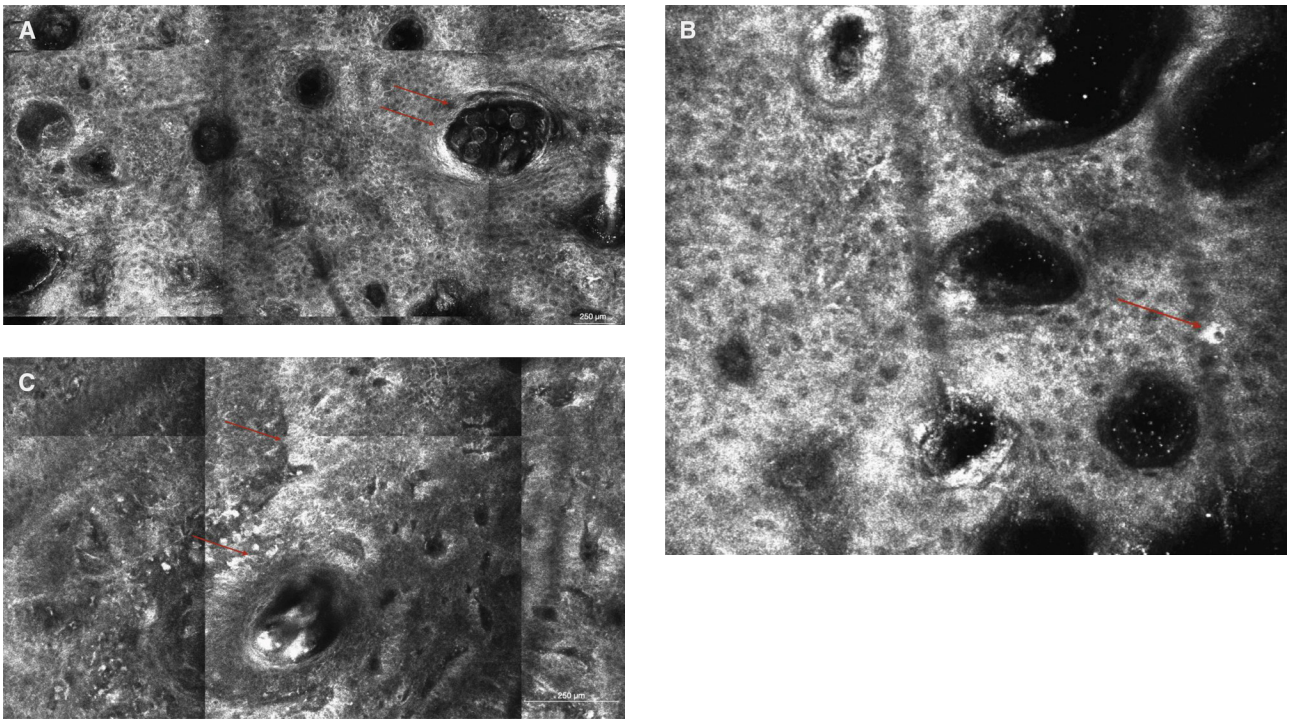

Figure 7. (A) RCM imaging of the case in Figure 6. Dysplastic keratinocytes in the epidermis. The follicle appears free from cellular infiltrate, and in this case, by chance, Demodex tales are visible (red arrows). (B) RCM single image at the level of the spinous/granular layer of the case in Figure 6. A roundish nucleated cell (red arrow) in the epidermis; differential diagnosis includes a severely dysplastic keratinocyte vs atypical melanocyte. (C) RCM mosaic at the level of the dermo-epidermal junction of the case in Figure 6. A roundish nucleated cell in the epidermis (red arrow); differential diagnosis includes a severely dysplastic keratinocyte vs atypical melanocyte.

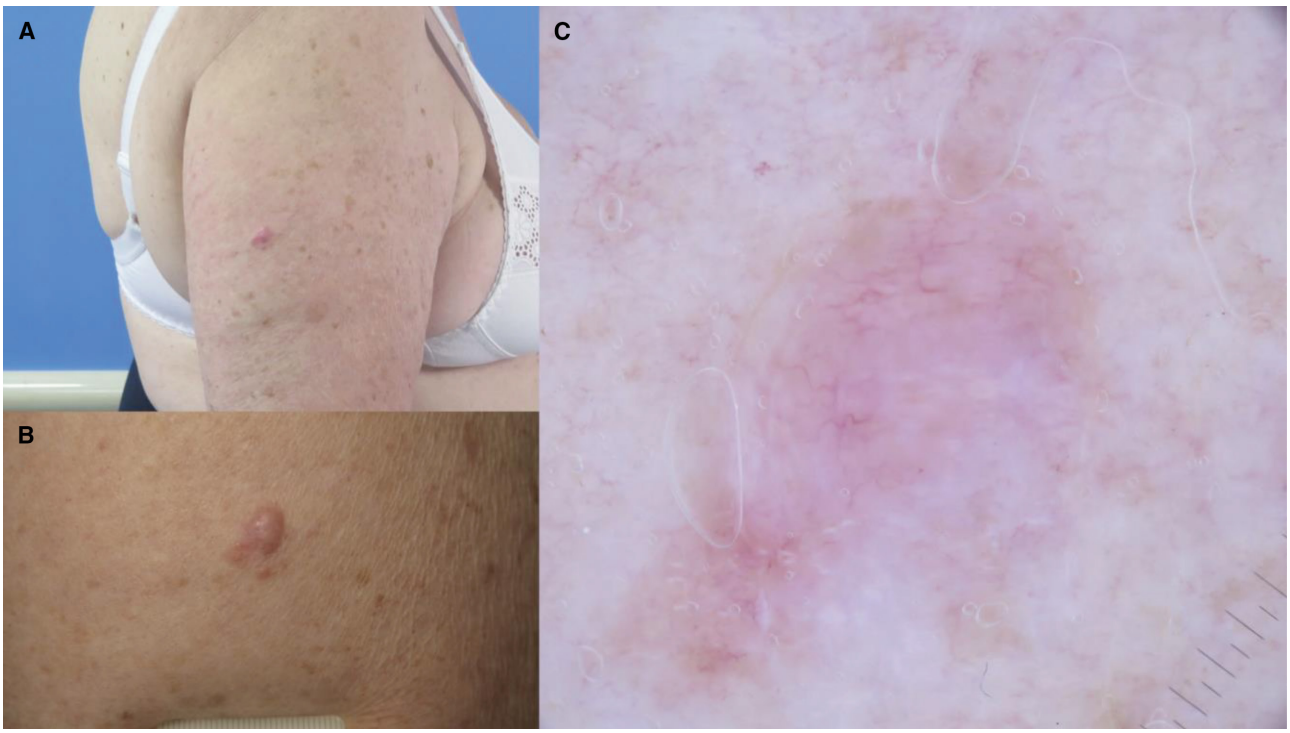

Figure 8. Amelanotic melanoma 5.3 mm Breslow thickness. (A) A pink nodule on the arm of a 50-year-old lady. (B) Close-up of the lesion that was firm on palpation. (C) Dermoscopy shows pink background, white lines, and short telangiectasias.

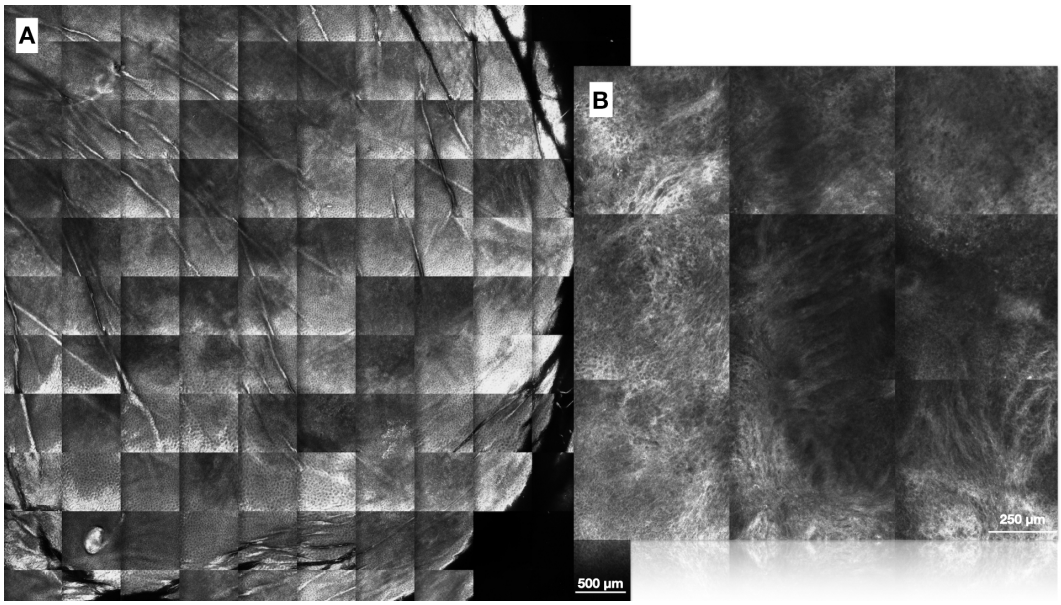

Figure 9. RCM imaging of case in Figure 8 (A) RCM mosaic shows regular honeycombed epidermis. (B) RCM mosaic at the level of the dermo-epidermal junction highlights a meshwork pattern.

Conclusions

Every tool is precious if it helps us recognize melanoma at an early stage and avoid unnecessary excisions. However, knowing when a tool can be really helpful, and when it is not, is very important for a good patient referral. We can summarize when an RCM examination is not warranted with a few indications:

1. Do not send halo nevi to RCM.
2. Do not expect RCM to solve the problem of dysplastic nevi vs early melanoma.
3. Spitz nevi should be managed based on clinical criteria (age).
4. Pigmented AKs can be a pitfall in RCM.
5. Acral, hyperkeratotic, ulcerated lesions are simply not visible under RCM.
6. Hypomelanotic lesions require experience to be evaluated in RCM.
7. Atypical lentiginous proliferations can present only very subtle features in RCM.

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