Dark pigmented lesions: Diagnostic accuracy of dermoscopy and reflectance confocal microscopy in a tertiary referral center for skin cancer diagnosis

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Background: There is lack of studies on the diagnostic accuracy of dermoscopy and reflectance confocal microscopy (RCM) for dark pigmented lesions.

Objective: To assess the diagnostic accuracy of dermoscopy plus confocal microscopy for melanoma diagnosis of dark pigmented lesions in real life.

Methods: Prospective analysis of difficult dark lesions with clinical/dermoscopic suspicion of melanoma referred for RCM for further analysis. The outcome could be excision or dermoscopic digital follow-up.

Results: We included 370 clinically dark lesions from 350 patients (median age, 45 y). Because of the clinical/dermoscopic/RCM approach, we saved 129 of 213 unnecessary biopsies (specificity of 60.6%), with a sensitivity of 98.1% (154/157). The number needed to excise with the addition of RCM was 1.5 for melanoma diagnosis.

Limitations: Single institution based; Italian population only.

Conclusions: This study showed that RCM coupled with dermoscopy increases the specificity for diagnosing melanoma, and it helps correctly identify benign lesions. Our findings provide the basis for subsequent prospective studies on melanocytic neoplasms belonging to patients in different countries. (J Am Acad Dermatol 2021;84:1568-74.)

Key words: dermatoscopy; diagnosis; melanocytic; melanoma; nevus; noninvasive; reflectance confocal microscopy.

Pigmentary traits are strongly linked to the colors of acquired melanocytic nevi and melanoma[1,2] and, thus, should be considered in the context of a diagnostic approach.

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Funding sources: This work was supported in part by research project NET-2011-02347213, Italian Ministry of Health. The funding source was not involved in the design and conduct of the study, collection, management, analysis and interpretation of data, preparation, review, or approval of the manuscript, or decision to submit the manuscript for publication.

Conflicts of interest: None disclosed.

IRB approval status: Reviewed and approved by the IRB of Azienda Unità Sanitaria Locale—IRCCS di Reggio Emilia, Italy (protocol number no. 2011/02347213).

Accepted for publication July 23, 2020.

Reprints not available from the authors.

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Published online July 27, 2020.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.07.084

The dermoscopic assessment of skin lesions is based on colors that are due to the presence of pigmented melanocytes or pigment-laden melanophages at different levels of the skin. Black and brown are due to pigmentation within the epidermis and are the most common colors seen in nevi with a prevailing epidermal component.[3]

As a matter of fact, individuals with different skin types are prone to different nevus types in terms of pigment distribution, color, and, to some extent, global dermoscopic pattern. Specifically, in skin type I, the prevalent nevus type is characterized by pink to light brown, whereas in skin type IV, nevi are dark brown.[1,4,5]

Although several studies have been focused on the characterization of amelanotic/hypomelanotic melanocytic and nonmelanocytic lesions,[6-10] little is known about the diagnostic performance of imaging devices for dark pigmented tumors.

Reflectance confocal microscopy (RCM) has been extensively applied in clinical practice in the diagnostic workflow of skin cancer.[11-16]

An RCM device is based on the inner reflectivity of cell structures, with melanin being one of the strongest sources of contrast. Microscopic tissue elements reflect light with different refractive indices, resulting in a gray scale of highly refractile structures. Given the high reflective index of melanin, RCM can be successfully used in highly pigmented tumors.[17]

The aim of the current study was to prospectively assess the diagnostic accuracy for melanoma of dermoscopy plus RCM in dark lesions in the clinical setting.

CAPSULE SUMMARY

- Dark pigmented lesions can be challenging based on clinical and dermoscopic examination only.
- The integration of reflectance confocal microscopy for 370 dark pigmented lesions with clinical and dermoscopic suspicion for melanoma allowed us to save 60.6% of unnecessary excisions while improving the number needed to excise.

METHODS

This was a prospective study performed between January 1, 2014, and December 31, 2018, and was approved by the institutional review board of Azienda Unità Sanitaria Locale—Istituto di Ricovero e Cura a Carattere Scientifico di Reggio Emilia, Italy (protocol number no. 2011/02347213).

Inclusion criteria were consecutive patients with at least 1 clinically dark pigmented lesion with clinical and dermoscopic suspicion for melanoma that was analyzed by means of RCM.

Exclusion criteria were the following: lesions with clear-cut features of malignancy, highly regressive/recurrent/collision tumors, acral lesions, and cases with poor-quality images or lacking confocal imaging.

Patient age, sex, phototype, number of nevi (<50, 50-100, or >100), body site (documented as head and neck, trunk, or upper and lower limbs), clinical management (surgical excision or follow-up), and histologic or clinical diagnosis after follow-up were recorded.

Dermoscopic analysis was rendered based on the revised 7-point checklist score,[18] whereas for RCM, the 4 diagnostic key features for skin cancer were evaluated.[19]

Histopathology was considered as the criterion standard diagnosis. Lesions that were not excised were followed up for dermoscopic digital monitoring at 3 and/or 6 months and at 1 year after the baseline visit. Lesions with significant dermoscopic changes[20] were excised, and the histopathologic diagnoses were collected. Subsequently, after surgical removal or follow-up, each lesion was classified as benign or malignant.

Imaging devices

Clinical and dermoscopic images were captured with a Canon (Tokyo, Japan) G16 camera with Dermlite Photo 10-fold magnification (3Gen, San Juan Capistrano, CA). Images were taken in polarized mode. Reflectance confocal imaging was obtained by using 2 different devices: an arm-mounted RCM and/or a handheld RCM device (VivaScope 1500 and/or 3000; Mavig, Munich, Germany).

Statistical analysis

Absolute and relative frequencies were calculated for qualitative variables; quantitative variables were assessed for normal distribution, and means ± standard deviations or median values with interquartile ranges (IQRs) were calculated.

To define the utility of the integrated clinical/dermoscopic/RCM approach in proper management, each case was classified as *lesion to excise* or *lesion not to excise*. We included in the lesions to excise both malignant tumors (melanoma, basal cell carcinoma, and melanoma metastasis) and benign lesions routinely excised in clinical practice (ie, Spitzoid-looking lesions).[21,22]

Abbreviations used:

IQR: interquartile range
NNE: number needed to excise
RCM: reflectance confocal microscopy

Sensitivity and specificity were calculated, together with the number needed to excise (NNE), calculated as the ratio between benign and malignant lesions excised.[16]

Statistical analyses were performed using the IBM SPSS, version 26.0 package (IBM, Armonk, NY).

RESULTS

Study population

A total of 370 dark pigmented lesions from 350 patients with clinical-dermoscopic suspicion of melanoma were referred for RCM examination. Patient and tumor characteristics are provided in Table I.

The majority of patients had skin type III (n = 219; 62.6%), followed by skin type II (n = 112; 32%), skin type IV (n = 14; 4%), skin type I (n = 4; 1.1%) and skin type VI (n = 1; 0.3%). Twenty-seven out of 348 (7.8%) patients had a history of melanoma. Regarding the total number of nevi, 215 (61.4%) patients had fewer than 50 nevi, 83 (23.7%) had 50 to 100 nevi, 27 (7.7%) had more than 100 nevi, and for 25 patients (7.1%), this aspect was not assessed.

The majority of lesions were located on the trunk (157 lesions; 42.4%), followed by the lower limbs (108 lesions; 29.2%), head/neck (63 lesions; 17%), and upper limbs (42 lesions; 11.4%).

Histopathologic diagnoses were melanoma (n = 89; 35.5%), common nevi (n = 80; 31.9%), Spitz/Reed nevi (n = 49; 19.5%), solar lentigo/seborrheic keratoses (n = 6; 2.4%), angiomas (n = 5; 2.0%), basal cell carcinomas (n = 17; 6.8%), melanoma metastasis (n = 2; 0.8%), and other benign lesions (n = 1 eccrine poroma, n = 1 endometriosis, and n = 1 vulvar melanosis; 1.2%).

Considering 89 melanomas, the median Breslow thickness was 0.9 mm (IQR, 0.5-1.4); 19 (21.3%) were in situ, 41 (46.1%) were equal or less than 1 mm, 14 (15.7%) were between 1 and 2 mm, 12 (13.5%) were between 2 and 4 mm, and 3 (3.4%) were greater than 4 mm.

Six out of 89 (6.7%) melanomas were nevus associated.

According to the final diagnosis (histologic or after follow-up), we considered 157 lesions as lesions to excise, including all 108 malignant lesions (melanomas, melanoma metastasis, and basal cell carcinoma) plus 47 of 49 Spitz/Reed nevi, 1 cutaneous endometriosis, and 1 eccrine poroma and 213 as "lesions not to excise" including 199 common nevi (of which 119 were not excised during

Table I. Patient demographic data and clinical and dermoscopic characteristics of the lesions

Variables	Value
Demographic/clinical characteristics	
Median age, y, (IQR)	45 (29-61)
Sex, n (%)	
M	172 (49.1)
F	178 (50.9)
Phototype, n (%)	
I	4 (1.1)
II	112 (32.0)
III	219 (62.6)
IV	14 (4.0)
VI	1 (0.3)
Number of nevi, n (%)	
<50	215 (61.4)
50-100	83 (23.7)
>100	27 (7.7)
Missing data	25 (7.1)
Total	350
History of previous melanoma, n/total (%)	27/348 (7.8)
Body site, n (%)	
Head and neck	63 (17.0)
Trunk	157 (42.4)
Upper limbs	42 (11.4)
Lower limbs	108 (29.2)
Total	370
Final diagnosis, n (%)	
Histopathologically verified	
Melanoma	89 (35.5)
Nevus	80 (31.9)
Spitz/Reed	49 (19.5)
Basal cell carcinoma	17 (6.8)
Solare lentigo/seborrheic keratosis	6 (2.4)
Angioma	5 (2.0)
Melanoma metastasis	2 (0.8)
Other benign*	3 (1.2)
Total	251 (67.8)
Not excised	119 (32.2)
Total	370 (100)
Dermoscopy	
7-PCL criteria, n (%)	
Atypical network	290 (78.4)
Blue-white veil	163 (4.1)
Atypical vessels	41 (11.1)
Streaks	135 (36.5)
Blotches	60 (16.2)
Irregular dots and globules	81 (21.9)
Regression	82 (22.2)
Median 7-PCL score (IQR)	2 (1-3)

7-PCL, 7-Point checklist; *F*, female; *IQR*, interquartile range; *M*, male.
*Melanosis, eccrine poroma, and cutaneous endometriosis.

follow-up), 2 Spitz/Reed nevi with no atypical features, and all benign nonmelanocytic tumors (solar lentigo/seborrheic keratosis, angiomas, and vulvar melanosis: n = 12).

Dermoscopic analysis

Regarding dermoscopic analysis, the median revised 7-point checklist score was 2 (IQR, 1-3), indicating a subset of difficult-to-diagnose lesions in both groups, with a score of 3 (IQR, 2-4) in lesions to excise and 2 (IQR, 1-3) in lesions not to excise (Fig 1 and Table I).

Atypical network was the most frequent criterion in both lesions to excise (n = 140/157; 89.2%) and lesions not to excise (n = 150/213; 70.4%) ($P < .001$); notably, it was observed in 93.3% (n = 83/89) of melanomas but also in 70.9% (n = 141/199) of melanocytic nevi and in the great majority of Spitz/Reed cases (85.1% of *to excise* and 100% of *not to excise* Spitz/Reed nevi).

RCM analysis of melanoma cases

With regard to RCM, overall, nevi showed a regular architecture and the absence of atypical cells, whereas in melanomas, RCM diagnostic features were present (Fig 2). If we examine analytically, the 4 RCM key features at baseline were identified in all but 5 melanomas (94%).

In detail, 2 cases (stage pT0 and stage pT1A) showed a verrucous/hyperkeratotic surface in the central area of the tumor, hampering the assessment of cellular details, and disarray, with the exception of focal peripheral large atypical melanocytes (Fig 3). Two melanomas (both stage pT1A) displayed a peripheral symmetric rim of dense nests and, thus, were judged as benign.

All 5 melanomas with few RCM features were correctly excised because of the integrated clinical and dermoscopic context.

Diagnostic accuracy of the clinical/dermoscopic/RCM approach

All 370 cases would have been excised based on clinical/dermoscopic examination alone.

This means that all lesions to excise would have been correctly identified (157/157; sensitivity, 100%), and no unnecessary excisions would have been saved (0/213; specificity, 0%).

With the additional integrated use of RCM in our clinical practice, we were able to save the unnecessary excision of 129 of 213 benign lesions (specificity, 60.6%) and correctly schedule 154 of 157 lesions for excision (sensitivity, 98.1%).

During follow-up (median of 4.2 months), 13 of 132 cases were excised (7 common nevi, 2 Spitz/Reed nevi, 1 vulvar melanosis, and 3 melanoma cases: 2 in situ and 1 invasive with 0.6-mm Breslow thickness).

Therefore, the NNE was 2.4 (262/108 lesions) with clinical/dermoscopic examination alone, and with the addition of RCM, it was 1.3 (133/105 lesions). Focusing on melanoma diagnosis, we obtained a reduction of NNE from 2.9 (262/89) to 1.5 (133/86), thanks to the integration of RCM.

DISCUSSION

Our study confirms the data on the distribution of dark lesions according to skin types. In line with previous studies,[1,5] dark lesions were more frequently associated with skin type III (62.6%) although present in skin type II in a percentage of cases. Interestingly, dark, difficult-to-diagnose lesions were found in patients with relatively few nevi; in fact, the majority of patients (61.4%) had fewer than 50 nevi.

This nevus distribution shows that difficult-to-diagnose dark lesions are solitary outlier lesions and, thus, look worrisome from both patients' and doctors' perspectives. With regard to age, dark pigmented lesions referred for RCM examination belonged to young adults. According to the literature data,[23] the pigmentation of nevi tends to decrease in elderly individuals, and thus, the problematic scenario of dark lesions is related to younger middle-aged patients and should be considered specifically in this patient subset, in which pigmented lesions represent a common situation.

Interestingly, the majority of melanoma were de novo tumors and not nevus associated. Although tumor pigmentation has not been analyzed according to melanomas status in relation to a pre-existing nevus, our study corroborates the hypothesis that almost 70% of melanomas arose de novo.[24-26]

In our study, all lesions were clinically and dermoscopically suspicious for melanoma diagnosis, but they showed a median 7-point checklist revised score of 2. Dermoscopy improves our diagnostic accuracy and the recognition of melanoma in the clinical setting, but in the presence of dark pigmentation, some criteria might be less visible, resulting in the excision of numerous benign lesions. A growing body of literature data shows that RCM can explore a given lesion in detail, revealing cytologic and architectural features regardless of the pigmentation.[12,14,16,17]

A key finding of our study is that the use of RCM permits to us to save 60.6% of unnecessary surgical excisions of dark pigmented lesions. The integrated clinical/dermoscopic/RCM approach changed the

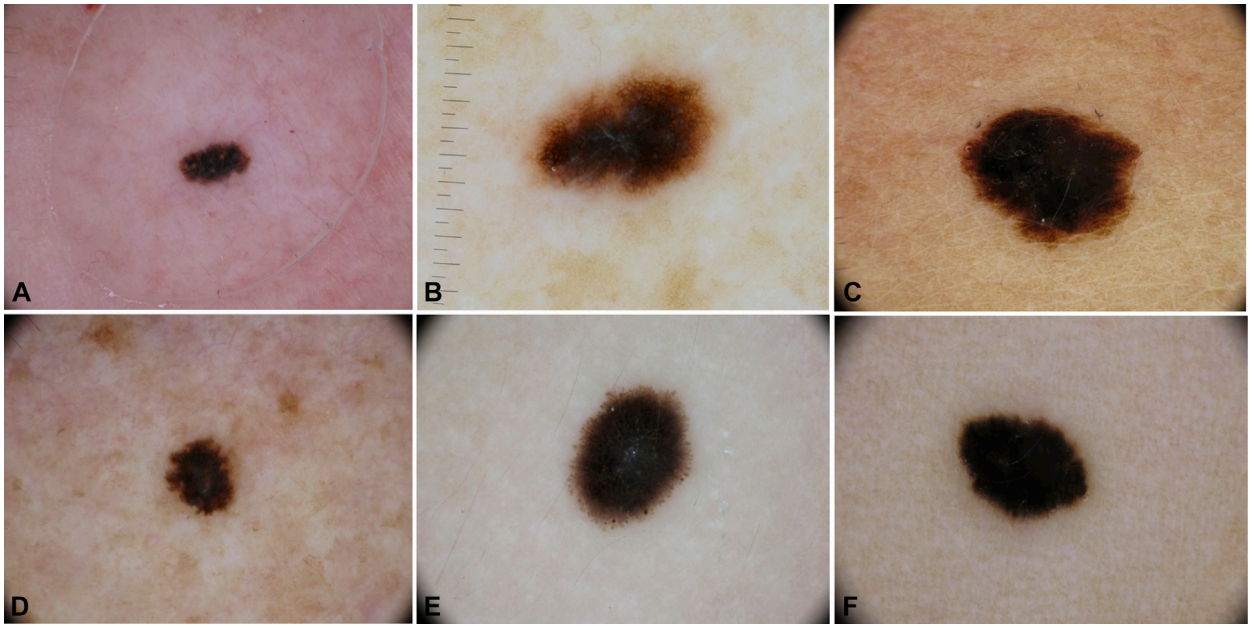

Fig 1. Dermoscopic images of dark pigmented lesions of (**A-C**) melanomas and (**D-F**) nevi.

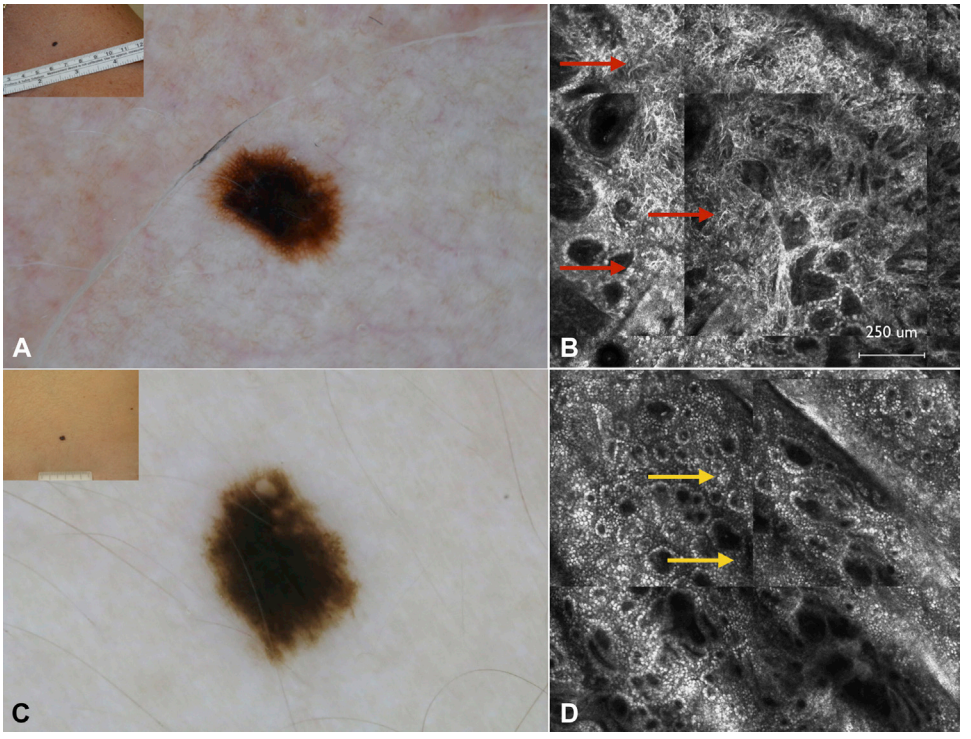

Fig 2. A paradigmatic example of a (**A**) a melanoma and (**C**) a nevus with similar clinical (inset) and dermoscopic aspects. **B**, A reflectance confocal microscopy image of the case in **A** shows cytologic atypia at the dermoepidermal junction (red arrows). **D**, A regular ringed pattern (yellow arrows) is visible in the case in **C**.

NNE from 2.9 to 1.5 for melanoma diagnosis; this is in line with previous prospective studies that did not specifically analyze the lesions according to pigmentation.[12,13,16]

Almost all melanomas (96.6%) were diagnosed by using the integrated approach (clinical/dermoscopic/RCM); only 3 false negative cases at baseline were detected afterward at digital follow-up.

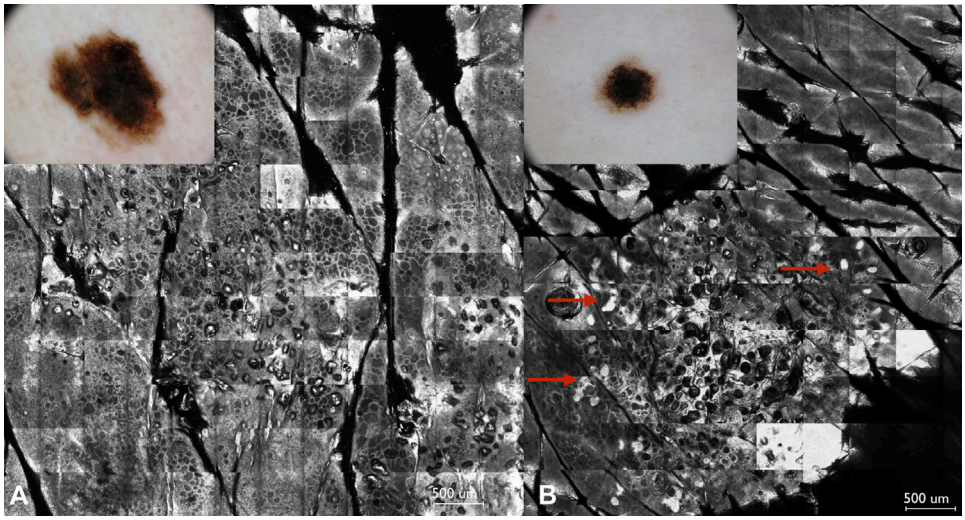

Fig 3. Two cases of melanomas with few reflectance confocal microscopy features at baseline, typified by (**A**) a hyperkeratotic surface and (**B**) in case 2, a regular rim of dense nests (red arrows).

Interestingly, 5 melanomas were not considered as suspicious based only on RCM findings at baseline, although all of them were correctly excised. These cases were mainly typified by the presence of a hyperkeratotic surface. Literature data on seborrheic-like lesions with a verrucous surface show a sensitivity for dermoscopy of 74.5%,[26] superior to clinical examination. For RCM, few data[27,28] are currently available, but these melanomas could be challenging if not evaluated in the overall clinical context (ie, new or solitary lesions). The other 2 melanomas that showed few RCM findings showed a rim of symmetrically and peripheral distributed dense nests. In general, a regular rim of dense nests on RCM indicates a 5-fold lower risk for melanoma,[15] and thus, in light of these data, the RCM reader was not so confident.

However, in all cases, a correct melanoma diagnosis was rendered because of the real-life examination of patients and lesion morphology. Spitz nevi were routinely excised in our clinical setting when present in patients older than 12 years or even in the younger age group if atypical clinically,[22] and thus, we have a high number of these nevi among the lesions to excise. In fact, so far, no reliable clinical data (dermoscopy and/or RCM) permits us to discriminate between a Spitz nevus and a Spitzoid melanoma based only on morphology.

Our study shows that dark lesions arising in patients with skin type III with few or a moderately low number of nevi represent a challenging scenario in the real clinical setting. The combined 3-phase simultaneous clinical/dermoscopic/RCM approach is an efficient workup to detect melanomas but, even more, to spare the unnecessary excision of benign lesions while improving the NNE.

The limitations of our study include the single institution–based population and the fact that the geographic distribution was limited to Italian patients.

In the era of the COVID-19 pandemic and, possibly, other similar future worldwide situations, dermoscopy and RCM imaging could be ideally implemented in a telemedicine setting[29] with a dedicated platform that allows patient imaging and diagnosis by distant doctors located in a hub hospital.

Furthermore, recent data show promising results on the application of machine learning algorithms[30] for melanoma and skin cancer diagnosis that could be of help for dark lesions or any other challenging scenario.

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