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"Twin lesions": Which one is the bad one? Improvement of clinical diagnosis with reflectance confocal microscopy

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ABSTRACT

Background: In vivo reflectance confocal microscopy (RCM) is a novel non-invasive diagnostic tool, which is used to differentiate skin lesions. Even in lesions with similar dermatoscopic images, RCM may improve diagnostic accuracy.

Methods: Three sets of false ''twin lesions" with similar macroscopic and dermatoscopic images are matched. All lesions are evaluated with RCM and lesions are excised for further evaluation. Corresponding features in confocal images, dermatoscopy and histopathology are discussed.

Results: In all matched pairs, one of the lesions was diagnosed as melanoma with the observation of melanoma findings such as: epidermal disarray, pagetoid cells in epidermis and cellular atypia at the junction. Benign lesions were differentiated easily with RCM imaging.

Conclusion: Examining dermatoscopically difficult and/or similar lesions with RCM facilitates diagnostic and therapeutic decision making. Using RCM in daily practice may contribute to a decrease in unnecessary excisions.

Introduction

Most non-skin cancers have shown decreased mortality over the past several decades, but the incidence and mortality of melanoma has continued to grow [1]. While early recognition and complete excision of a melanoma is curative, advanced stages remain associated with high mortality rate, despite the progress in treatment modalities. The challenge is to make

an accurate diagnosis and to identify all of the malignant lesions while avoiding unnecessary surgical procedures in benign lesions.

Dermatoscopy is a widely used, reproducible method, which facilitates the differentiation of benign and malignant melanocytic and non-melanocytic lesions, especially in the hands of dermatologists [2-4].

The accuracy of melanoma detection thanks to dermoscopy has been widely investigated. Characteristic dermoscopic features for melanoma are: atypical network, blue-white veil, atypical vascular pattern, irregular dots and globules, irregular streaks, irregular blotches, and regression structures [2,5,6]. Pattern analysis, the ABCD method, and the 7-point checklist scoring system of dermatoscopic characteristic features and clues significantly increase the diagnostic accuracy, however, they leave a not so small number of difficult lesions for excision [3,7,8].

In a systematic review over 10 years, it is reported that in skin cancer centers where dermoscopy is routinely used in practice, 76,783 nevi have been excised and among them 9,910 melanomas were detected [7].

In the case of clinically and dermatoscopically challenging lesions, in vivo reflectance confocal laser microscopy (RCM) may offer the possibility of non-invasive investigation of a lesion and improving the specificity of melanoma diagnosis [9]. RCM allows optical imaging with resolution similar to histology and good contrast, which makes imaging of the cellular architecture of epidermis and the superficial dermis (up to 250 µm) possible [10].

Herein, we describe and discuss three sets of dermatoscopically "twin" lesions, where clinical and dermoscopic images overlap and might confound the real diagnosis. All of these similar lesions were excised and the diagnosis was histologically confirmed. In every twin pair, one of the lesions was a melanoma. RCM improved diagnostic accuracy and helped decisively in setting the correct diagnosis in all of the lesions examined.

Lesion imaging was performed using high quality digital polarized dermatoscopic photos (DermLite FOTO System [3Gen Inc, San Juan Capistrano, CA] and FotoFinder Medicam [FotoFinder Systems GmbH, Bad Birnbach, Germany]) and a commercially available RCM device (Vivascope® 1500, Mavig GmbH, Munich, Germany). VivaScope 1500 provides basic images with a 500 × 500 mm horizontal field of view with an imaging depth of approximately 200–250 µm, usually correlating to the upper dermis [10]. Image acquisition requires a few minutes and is completely harmless for the patient.

Cases 1 & 2

Patient 1 was a 54-year-old female who was referred to the dermatology department because of a congenital nevus in which the patient herself had noticed enlargement and darkening in color during the past month. Bleeding was not reported. The lesion was a 1.8 x 1.5 cm large macule with a central nodular component and was located on the dorsal surface of her left lower leg (Figure 1a). A mild thickened crusty appearance was present. Dermatoscopically, it exhibited more than one color (light and dark brown, white and pink). An atypical, reticular pattern was predominant with an inverse network. Asymmetrically distributed dots and globules were observed (Figure 1b). The dermatosurgeons were hesitant to perform a complete excision on the lower leg for a possibly benign lesion.

Patient 2 was a 76-year-old female with a recently growing lesion on the anteromedial side of her right lower leg. She could not provide details on the lesion's history, having noticed it recently. Macroscopically, it was a brown and slightly elevated 1.9 cm large macule (Figure 1e), with a mildly thick surface. The differential diagnosis was a pigmented Bowen's disease, seborrheic keratosis and lentigomaligna-melanoma. Under dermoscopy, the lesion revealed multiple colors (light and dark brown, white, pink). It was composed of a brown structureless background with white lines. A network was not clearly recognizable. Brown globules were distributed unevenly on the lesion. Some milia like cysts were also present (Figure 1f).

These clinically and dermatoscopically similar lesions were further investigated with RCM. Lesion 1 showed epidermal disarray with pagetoid infiltration. Pagetoid cells are large, with bright cytoplasm and dark nuclei, and represent one of the most common findings in melanoma [10] (Figure 1c). An atypical honeycombed pattern was dominant in the epidermis, while the dermal-epidermal junction (DEJ) showed a non-specific pattern. Vascular structures were identified. The lesion was then excised with a pre-diagnosis of melanoma. Histopathologic examination confirmed RCM findings and the patient was diagnosed with superficial spreading melanoma, Clark-Level III with a thickness of 0.85 mm and 0 mitoses per/mm^2 (Figure 1d).

RCM of patient 2 showed the innocent picture of elongated cords and bulbous projections (Figure 1f). Corneal plugs and keratin filled invaginations were conspicuous. Cells around the pseudofollicular openings were monomorphic in structure. These features were consistent with seborrheic keratosis so that a shave excision was performed. Histopathological examination confirmed the diagnosis of a seborrheic keratosis (Figure 1g).

Cases 3 & 4

Patient 3 was a 76-year-old male who was referred to the dermatology department with a lesion located on his left preauricular area. The lesion was asymptomatic for 10 years, however, the patient had recognized an increase in size recently.

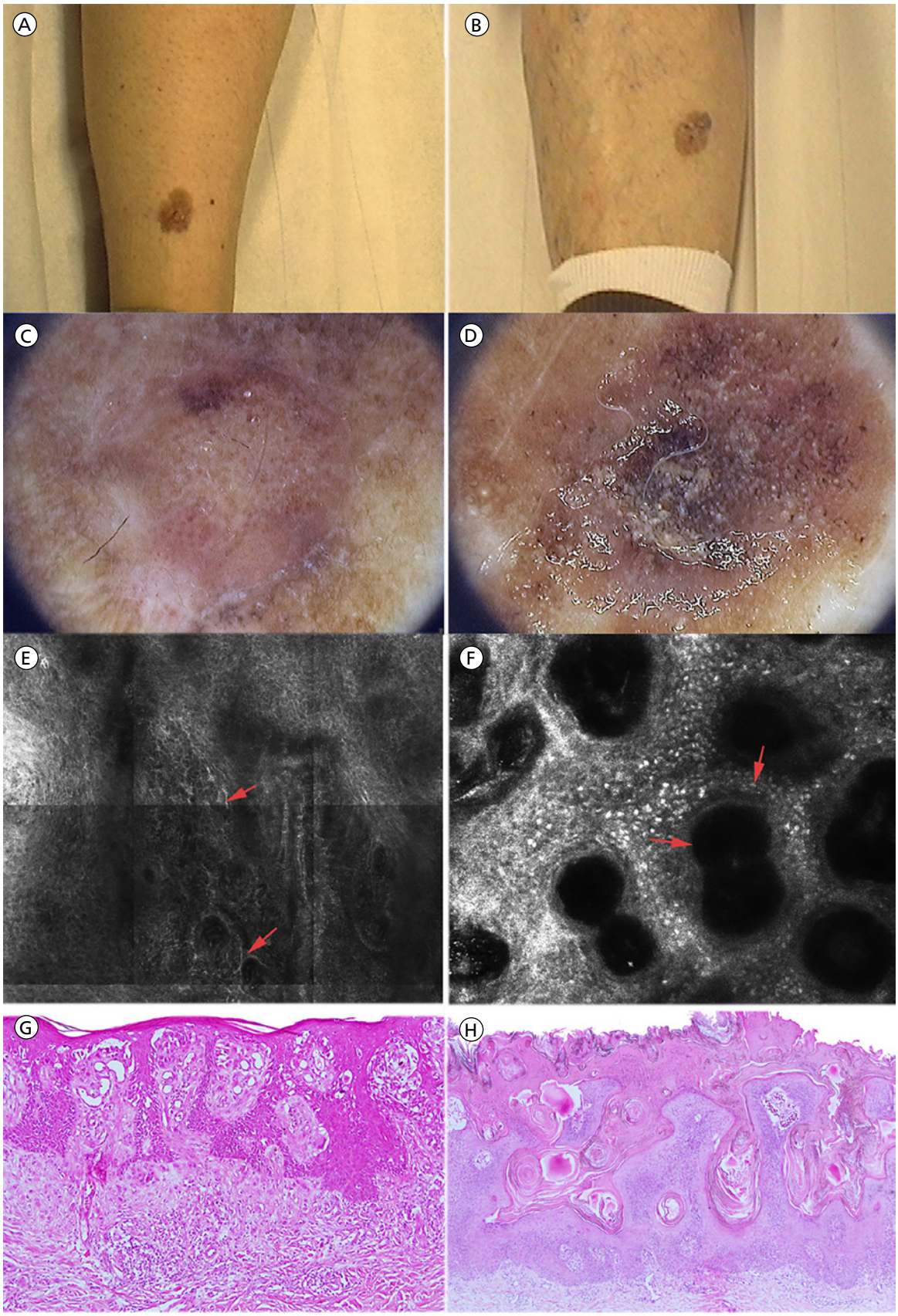

Figure 1. Hyperpigmented macular lesion on dorsal surface of leg (1a). Atypical dermoscopic view with more than one color and thick reticular lines in the periphery (1b), epidermal disarray with pagetoid infiltration (arrows) in confocal image (1c). Histologic examaination (H&E 100X): superficial spreading melanoma presenting atypical melanocytes, pagetoid spreading and horizontal confluence of the rete ridges in the dermis, few single-cell proliferates of atypical melanocytes, dense inflammatory infiltrate and solar elastosis (1d). Brown macular lesion on dorsal surface of leg (1e). Dermatoscopically, more than one colored lesion with brown globules and milia-like cysts (1f), pseudofollicular openings and elongated cords in confocal image (1g), papillomatous seborrheic keratosis (H&E 40X): massive hyperkeratosis and papillomatosis and horn cysts (1h). [Copyright: ©2017 Saral et al.]

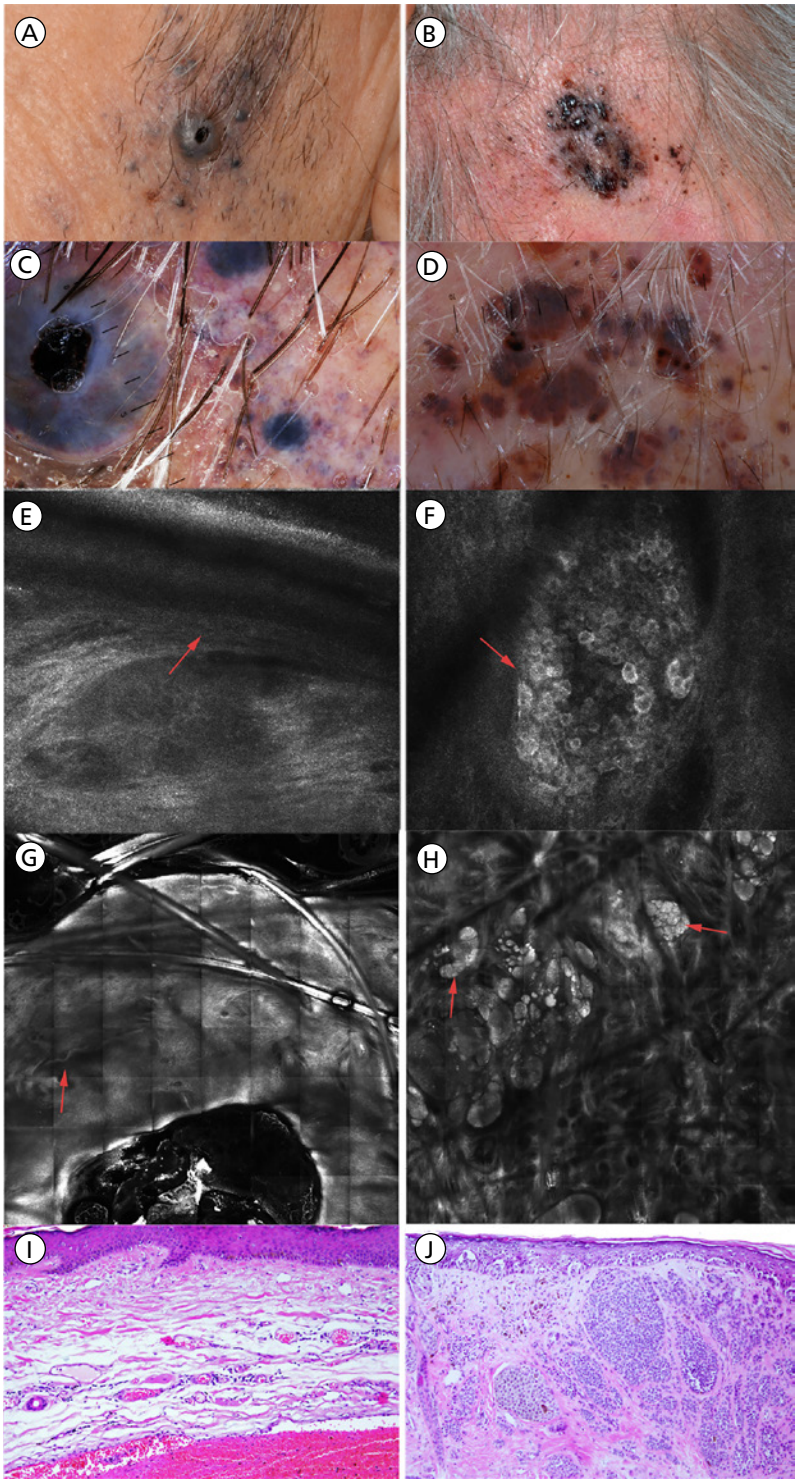

Figure 2. Blue central papule and numerous satellite papules (2a). Blue papule with a central hemorrhagic crust and on a shiny white structureless blue, black macule, serpentine and linear vessels (2b). Vivablock® (2d, 5x5 mm) and Viva image (2c) showing large spaces separated with thin septa. Histologic examination revealed, cavernous, arteriovenous, hemangioma (H&E 100X): a dermal lesion composed of large dilated and both thick and rather thin-walled vessels with a lumen composed of lobulated aggregates of poorly canalized blood vessels filled with erythrocytes (2e). Postauricular hyperpigmented lesion on macroscopic view (2f). Multiple blue-black blotches and asymmetrically distributed dots (2g), sheets of atypical cells forming sheet-like structures, the junction substituted with an unspecific pattern (2h). Dense and sparse nests with atypical cells (2i). Histologic examination revealed a superficial spreading malignant melanoma (H&E 100X): the epidermis presents atypical melanocytes in a pagetoid spread. In the dermis, besides the normal melanocytes gathered in nests that show signs of maturation, nests of atypical melanocytes and single-cell proliferates of atypical melanocytes are present. Solar elastosis and melanophages are in the upper dermis (2j). [Copyright: ©2017 Saral et al.]

Macroscopically, the lesion consisted of a central black colored 0.4 cm papule with central ulceration and numerous small satellite lesions around the central papule (Figure 2a). Dermatoscopically, it exhibited more than one color (black, blue, white, gray). Red-bluish-black homogeneous areas were prevalent at the center, with a central hemorrhagic plug; at the periphery, shiny white structureless areas were present (Figure 2b). Serpentine and linear vessels constituted the vascular component. The patient was presented to the imaging outpatient clinic for further diagnostics with the differential diagnosis of pigmented basal cell carcinoma, metastasizing blue nevus and hemangioma.

Patient 4 was a 75-year-old male with a lesion on the postauricular area of the scalp. He had noticed the lesion was pruritic recently. Macroscopically, the lesion consisted of numerous black colored papules and brown-colored macules (Figure 2f). Dermatoscopic pattern consisted of brown to blue to black blotches, with asymmetrically distributed dots and globules of various sizes and colors (Figure 2g). Vascular structure was indistinguishable.

Before proceeding with surgical procedures, both lesions were examined with RCM. In vivo reflectance confocal imaging of patient 3 showed vascular, large, dark spaces separated by thin, bright septa. In real-time imaging, vascular flow with moving small round bright blood cells were clearly seen (Figure 2c, 2d). Atypical cells were not present. RCM imaging favored the diagnosis of an angioma. Histopathologic examination with hematoxylin-eosin staining (H&E) showed a cavernous arteriovenous hemangioma (Figure 2e); staining with alpha-smooth muscle and actin showed wide, dilated, lagoon-like vessels presenting a continuous rim of alpha-smooth muscle actin-positive pericytes, which confirmed previous evaluations.

Lesion 4 showed a disarray of the normal architecture of the epidermal superficial layers, characterized by unevenly distributed bright granular particles and cells, irregular in shape and size (Figure 2i). A honeycombed or cobblestone pattern was

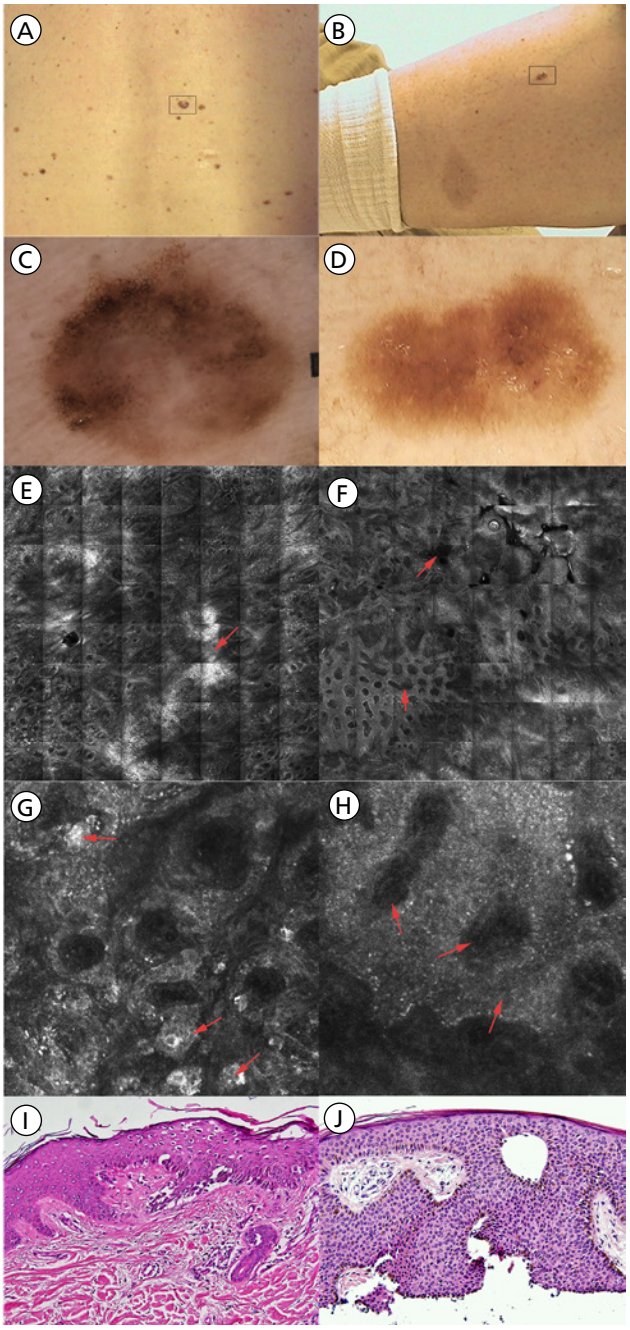

Figure 3. Hyperpigmented macule on back (3a), asymmetrical globular lesion with more than one color, and inverse network (3b). Atypical cobblestone pattern in the epidermis with some pagetoid cells and dense and sparse nests were visible as dermal clusters of aggregated, pleomorphic cells (3c, 3d). Malignant melanoma (H&E 200X): superficial spreading melanoma with atypical melanocytes in a pagetoid spread as well as gathered in asymmetrical nests. In the dermis, inflammatory infiltrates with melanophages are present (3e). Hyperpigmented macule on lateral aspect of leg (3f). Dermatoscopically pseudo-reticular pattern with asymmetrically located dark brown structureless areas and thin reticular lines on left side (3g). Confocal view exhibiting elongated cords and bulbous projections, with branching tubular structures at the periphery, consistent with seborrheic keratosis and solar lentigo (3h, 3i), Histologic examination revealed seborrheic keratosis (H&E 200X) with acanthosis and papillomatosis of the epidermis and hyperpigmented keratinocytes presented in a pigmented seborrheic keratosis. In addition to that, remnants of the horn cysts are shown (3j). [Copyright: ©2017 Saral et al.]

not recognizable. Large bright cells with outlined border and dark nuclei, some of them with dendrites, were identified as round and dendritic pagetoid cells. The entire epidermis was replete with sheets of atypical cells (Figure 2h). The structure of the DEJ demonstrated evidences of remaining meshwork pattern, but it was mostly replaced by a non-specific pattern in which atypical pleomorphic melanocytes were distributed in sheet-like structures. Some irregular nests, variable in size and reflectivity, constituted dense and sparse nests. Based on these findings, strikingly suggestive for malignancy, the entire lesion was excised. The patient was diagnosed with superficial spreading melanoma, Clark-Level IV with a tumor thickness of 3 mm, mitosis rate 3 per/mm^2 and signs of regression (Figure 2j).

Cases 5 & 6

Case 5 was a 52-year-old man, referred to the hospital with a history of superficial spreading melanoma and a nevus with a change of color noticed during the previous month (Figure 3a). The lesion, located on the right side of his back, was asymmetrical in color and 1 cm in diameter. Dermatoscopic examination revealed a prominent globular patterned lesion with inverse network on the inferior side (Figure 3b). On the superior portion, peripherally located asymmetrical thick reticular lines were areas of concern. Atypical vessels were also noticed.

Case 6 was a 62-year-old male patient referred to the dermatology department because of a newly arisen pigmented lesion (Figure 3f). Macroscopically, a brown asymmetrical 0.8 cm large macule was observed on the lateral side of his left lower leg. Dermatoscopically, a pseudo-reticular pattern was predominant, with asymmetrically located dark brown structureless areas at the bottom of lesion and thin reticular lines on the left side (Figure 3g).

Because of history and dermatoscopic features, both lesions were further imaged with RCM. Case 5 exhibited an atypical cobblestone pattern in the epidermis with some pagetoid cells and a disrupted ringed and meshwork pattern at the junction; dense and sparse nests were visible as dermal clusters of aggregated, pleomorphic cells. An increased vascular pattern was noticed in the superficial dermis (Figure 2c, 3d).

Case 6, on the contrary, showed elongated cords and bulbous projections, with branching tubular structures at the periphery, consistent with a seborrheic keratosis and solar lentigo (Figure 2h, 3i). Both lesions were excised because of the history of growth and histopathologic examination confirmed case 5 as a superficial spreading melanoma in situ (Figure 3e) in association with a compound congenital nevus and case 6 as a seborrheic keratosis (Figure 3j).

Discussion

The most important aspect of melanoma diagnosis is to recognize lesions at an early stage. Early melanoma lesions sometimes have non-specific features and are hard to determine with naked-eye examination. Introduction of handheld dermatoscopes and widespread use of dermatoscopy in skin cancer examination has improved specificity and sensitivity of melanoma diagnosis. However, dermatoscopic features of a melanoma are highly variable, and most of the time physicians have to excise many benign lesions in order to avoid a missed melanoma. Number needed to treat (NNT) is an effective value to measure melanoma detection accuracy. The abbreviation stands for number of pigmented lesions excised to detect one melanoma [11]. Carli et al reported decrease of NNT from 18 to 4.3 with dermatoscopic examination [12]. Rolfe calculated NNT in a dermatology clinic (with available dermatoscopes) as 11.9 by calculating the number of seborrheic keratoses, nevi and melanoma excised to detect one melanoma. The ratio to identify non-melanoma skin cancer was significantly lower (1.97), which means about one in every two excisions with a pre-diagnosis of non-melanoma skin cancer was accurate [13].

Reflectance confocal microscopic imaging is a promising non-invasive technique that facilitates the diagnosis of cutaneous melanoma and the discrimination of benign melanocytic lesions. RCM features and diagnostic criteria used in melanoma, melanocytic lesion, seborrheic keratosis and angioma diagnosis has been described [10,14-16]. Epidermal disarray, pagetoid cells in epidermis, non-edged papilla, cellular atypia at the DEJ, atypical nests and bright nucleated cells in the upper dermis are important findings in superficial spreading melanoma imaging. Two of the melanomas in our case series predominantly exhibited atypical pigment network on dermoscopy which corresponded to non-homogenous dermal papillae distribution and presence of irregular aggregates of cells in the interpapillary spaces with the RCM. The other melanoma had irregular globules and dots as the predominant pattern; the atypical globules correlate with dense and sparse nests of atypical melanocytes on RCM. Black dots in dermoscopy correlate with atypical cells in the epidermis. Non-edged papilla on RCM corresponds to dermal papillae without demarcated contours and bright, nucleated cells are roundish pagetoid cells on histopathologic examination.

On the other hand, RCM of seborrheic keratosis is visualized as corneal plugs, corneal cysts, surface holes and crypts. Elongated cords, which correspond to elongated rete ridges in histology, and bulbous projections and keratin-filled invaginations are observed. Cells are monomorphic in structure without architectural atypia. In our case series, case 3 was a cavernous arteriovenous hemangioma lesion. Real-time imaging is important in angiomatous structures to observe moving erythrocytes in between vascular dark spaces separated with thin septa. Dark spaces and thin septa correlate with dermal vascular proliferations with vascular spaces on histopathology.

Imaging with RCM is especially beneficial in distinguishing amelanotic melanoma and other clinically featureless melanomas with indistinct dermatoscopy [17-20]. Equivocal lesions with similar dermatoscopic findings are important challenges for dermatologists. Reflectance confocal microscopy is reported to be beneficial in discrimination of similar lesions such as: facial lentigo maligna vs. pigmented non-melanocytic macules and Spitz nevus vs. melanoma and other equivocal lesions [21-23].

Langley et al, when comparing diagnostic accuracy of RCM and dermatoscopy in a prospective examination, found sensitivity of 97% and specificity of 83% for RCM. When the two techniques were combined, none of the melanomas were missed [24]. Current literature highlights high sensitivity of RCM for recognizing melanoma [23-25]. Nevertheless, studies on RCM are mostly designed together with dermatoscopy and recommend integration of the two methods in the diagnostic process [23-26].

Several studies on the impact of addition of RCM showed increased cost effectivity and reduced NNT [25,27,28]. In a study by Pellacani et al, NNT was decreased to 4.3 from 14.6 and RCM analysis reduced the number of lesions for excision to less than half of the benign lesions (46.5%) without missing a melanoma [28]. Alarcon et al reported this decrease in a study with a different design from 3.73 to 2.87 [25].

In our case series, the integration of RCM in the diagnostic process was instrumental in determining the correct diagnosis where clinical and dermatoscopic patterns were overlapping and when it was difficult to discriminate between benign and malignant lesions. In particular, similar and difficult to interpret dermoscopic patterns were quickly guided to a correct diagnosis by RCM, in a time-sparing and efficient way for both clinician and patient.

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