Dermoscopy/Confocal Microscopy for Melanoma Diagnosis

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Abstract

The development of noninvasive diagnostic tools such as dermoscopy and reflectance confocal microscopy (RCM) has improved clinician accuracy for melanoma diagnosis. The effectiveness of these methods is due to their capacity to visualize malignant changes in the epidermis and upper dermis before such changes are visible to the naked eye. Melanomas and other lesions have characteristic features under both dermoscopic and confocal views that can distinguish them from each other and improve the rate of early detection and removal of malignant lesions. While general dermoscopic and confocal features of melanoma are based on the features of superficial spreading melanomas, continuing research has identified features of melanomas on unusual anatomic sites, such as the face or the mucosa, and different subtypes of melanoma, such as nodular and lentigo maligna.

Introduction

The development of noninvasive diagnostic tools such as dermoscopy and reflectance confocal microscopy (RCM) has improved clinician accuracy for melanoma diagnosis (Longo et al. 2013a; Segura et al. 2008). More recently developed methods include optical coherence tomography (OCT), multispectral computer analysis (MelaFind), Raman spectroscopy, and electrical impedance spectroscopy (EIS) with different evidence and applicability in melanoma diagnosis (Welzel and Schuh 2017). With the exception of dermoscopy, which allows a fast and reliable evaluation of almost all skin lesions, these new tools are limited to clinically selected lesions, thus representing a second

level of diagnosis for clinically and dermoscopically equivocal lesions.

Dermoscopy

Basics of Dermoscopy

Dermoscopy, also called dermatoscopy, epiluminescence microscopy, surface microscopy, or incident light microscopy, is a noninvasive diagnostic tool that significantly improves the diagnostic accuracy of melanoma compared to naked eye clinical examination (Braun et al. 2004; Kittler et al. 2002). Dermoscopy uses a handheld magnifying scope called a dermatoscope, which is illuminated either with polarized light or with non-polarized light plus an interface liquid. Magnification is between 6x and 100x, most commonly a 10x magnification. Dermoscopy is usually performed with a handheld lens, a dermoscopic lens fitted to a standard digital camera, or a digital dermoscope attached to a digital imaging system and is used to visualize surface and subsurface skin structures not visible to the naked eye. Many of these structures correspond to histopathological features and thus give information about the cellular nature of the lesion (Wolner et al. 2017). The polarized light or the non-polarized light plus an interface liquid (oil, alcohol, or gel) eliminate surface reflection to allow inspection of structures and blood vessels in the epidermis, the dermo-epidermal junction, and the superficial dermis (Soyer et al. 2001a). These two modalities are comparable in their ability to assess overall dermoscopic patterns; however, certain structures are better viewed by one or other. Non-polarized light allows better inspection of the superficial layers, allowing blue-white color caused by orthokeratosis and milia-like cysts to be more prominent. Polarized light is better at visualizing the deeper layers, allowing blood vessels, vascular blush caused by increased blood volume, and shiny white lines to be seen more easily. Shades of brown and blue also appear darker under polarized light. Blood vessels are more easily seen under polarized light because polarized light dermoscopes do not need to be in contact with the skin; even very light pressure on the skin from a non-polarized dermoscope with immersion fluid can compress the small vessels in the skin and make them invisible by reducing the amount of blood in them (Wang et al. 2012).

Timely diagnosis and treatment of melanoma during its earliest stages are crucial to patient survival, and the thickness of a melanoma at diagnosis strongly affects prognosis, with 5-year survival rates dropping steeply as thickness at diagnosis increases. Dermoscopy enables users to detect thin melanomas more frequently, by revealing early melanoma-specific signs not yet visible to the naked eye. A study of 347 melanoma patients found that the mean Breslow thickness of melanomas detected with dermoscopy was 1.40 mm, while those detected by naked eye examination had a mean Breslow thickness of 2.59 mm (Haenssle et al. 2015).

Diagnostic Accuracy of Dermoscopy

A meta-analysis (Vestergaard et al. 2008) of dermoscopy performed in clinical settings (that is, not image-based diagnosis with no patient contact) found that the melanoma diagnostic odds ratio was 9.0 times higher for dermoscopy compared to naked eye examination. The summary estimated sensitivity was 87% for dermoscopy and 69% for naked eye examination, while summary estimated specificity was not statistically different between dermoscopy and naked eye examination. Thus, dermoscopy improves physicians' ability to detect melanoma without increasing the number of benign lesions wrongly diagnosed as melanoma.

Therefore, dermoscopy improves the benign to malignant excision ratio, reducing associated surgical morbidity (Wolner et al. 2017). In one 10-year multicenter study, the benign to malignant excision ratio improved from 12.8:1 to 6.8:1 ($P < 0.001$) at specialist skin cancer sites, while there was no statistically significant change at other sites (31.9:1–28.5:1; $P = 0.45$), which the authors attributed to the uptake of dermoscopy at specialist skin cancer clinics (Argenziano et al. 2012).

Dermoscopy does require some training to achieve improved diagnostic accuracy. A meta-

analysis by Kittler et al. (2002) found that in untrained physicians, dermoscopy was no better than clinical examination at detecting melanoma, with log odds ratios of 2.5 and 2.0 for clinical examination and dermoscopy by non-experts, respectively ($P = 0.65$), and 3.8 for dermoscopy by experts ($P = 0.03$ and $P = 0.001$ compared to clinical examination and untrained dermoscopy, respectively). However, training need not be extensive, with short training modules improving sensitivity without compromising specificity (Argenziano et al. 2006; Rogers et al. 2016). Short intensive training modalities have been shown to improve the diagnostic accuracy of general practitioners and medical students, as well as dermatologists (Wolner et al. 2017). For example, after a 4-hour in-person group training on the use of ABCD in clinical examination and three-point checklist in dermoscopy for skin cancer detection, primary care practitioners using a dermoscope had better sensitivity than those using naked eye examination (79.2% vs 54.1%, $P = 0.002$) with no decrease in specificity (71.8% vs 71.3%) (Argenziano et al. 2006).

Dermoscopy is now widely used: 84% of attending dermatologists in the United States report using dermoscopy daily (Wolner et al. 2017); 88% of dermatologists in Europe reported using dermoscopy, with 84.9% of those using it daily (Forsea et al. 2017); and 95% of Australian dermatologists report using dermoscopy (Chamberlain and Kelly 2007). Many dermatologists using dermoscopy report receiving training in dermoscopy during their residency but also as further professional development from in-person or online dermoscopy courses, at conferences and congresses, from mentors and tutors, and from using books and atlases of dermoscopy (Forsea et al. 2017).

Reflectance Confocal Microscopy

Basics of Reflectance Confocal Microscopy

Reflectance confocal microscopy (RCM) is a noninvasive diagnostic tool that allows the observation of structures at a quasi-histopathologic resolution. For this reason, RCM is considered by some as a virtual biopsy.

RCM uses an 830 nm near-infrared diode laser light source. This laser source, which is harmless to the skin, emits light at a point of interest on the skin which afterward is backscattered. This light is later filtered through a pinhole which only collects light from the point of interest, thus allowing the alignment of the point of interest and the pinhole in the same focal plane (confocal) (Rajadhyaksha et al. 1999; Waddell et al. 2018). Since RCM images are grayscale, depending on the cellular refractive index, structures are brighter if their refractive index is high (i.e., melanin, keratin), whereas they are seen dark if their refractive index is low (i.e., water present inside the nuclei) (Rajadhyaksha et al. 1995).

Currently, two reflectance confocal microscopes are commercially available: a wide-probe microscope (Fig. 1a; Vivascope 1500, Caliber ID, Rochester, NY) and a handheld microscope (Fig. 1c; Vivascope 3000, Caliber ID, Rochester, NY). The wide-field confocal microscope requires attaching a metal ring onto the skin and allows the examination of lesions up to 8 × 8 mm by producing image mosaics by attaching multiple 500 μm individual images (Fig. 1b). The handheld confocal microscope allows freehand movement along the skin and can acquire single images of 0.75 × 0.75 mm or 1 × 1 mm (depending on the microscope generation) and videos. These videos, if taken at the same horizontal plane, can be stitched into videomosaics using a newly developed automated algorithm (Fig. 1d) (Kose et al. 2017).

These RCM microscopes can noninvasively obtain in vivo, real-time images and videos with a lateral resolution of 1 μm and 4 μm optical sectioning, which results in the visualization of cellular structures up to approximately 250 μm in depth (Rajadhyaksha et al. 1999). This allows an *en face* examination of the epidermis and the upper dermis with near-histological resolution.

Diagnostic Accuracy of Reflectance Confocal Microscopy

Like dermoscopy, RCM helps clinicians to detect early melanomas more easily and to reduce the benign to malignant excision ratio. In fact,

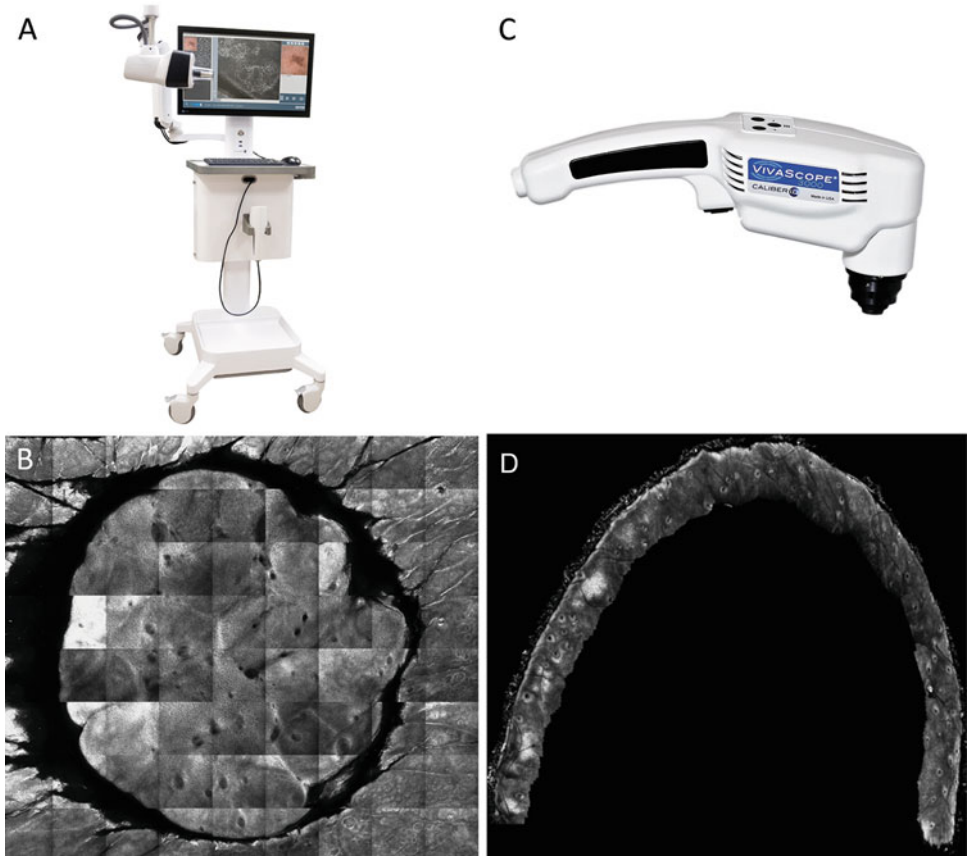

Fig. 1 RCM: currently two reflectance confocal microscopes are available: (**a**) a wide-probe device, Vivascope 1500 (Caliber ID, Rochester, NY) which allows the generation of 8 × 8 mm mosaics (**b**), and a handheld device (**c**), Vivascope 3000 (Caliber ID, Rochester, NY) which allows the acquisition of videos, still images, and videomosaics using specific software algorithms (**d**)

multiple studies have shown that reflectance confocal microscopy has very high diagnostic accuracy to identify skin cancers and particularly melanoma (Edwards et al. 2016; Xiong et al. 2017). Overall, the sensitivity and specificity for diagnosing melanoma with RCM are 91–100% and 68–98%, respectively (Que et al. 2016). This results in a number needed to excise (NNE) or benign to malignant ratio of around 1:1.8–1:2.4 (Alarcon et al. 2014b; Borsari et al. 2016; Yélamos et al. 2018b). RCM has been shown to be a very accurate tool to diagnose melanoma, even when evaluating lesions which are challenging clinically and dermoscopically. Therefore, RCM allows the detection of melanoma without excising more benign lesions. This is mainly due to the fact that RCM has near-histological resolution and can identify very small amounts of melanin which are not visible to the naked eye or even with dermoscopy (Rajadhyaksha et al. 1995).

Clinical Scenarios for the Use of Reflectance Confocal Microscopy

From a theoretical standpoint, RCM could be used in any equivocal clinical or dermoscopic lesion which is suspicious for a skin cancer. However, choosing which lesions or which patients should undergo RCM examination is crucial since RCM is currently restricted to a few centers and specialty skin cancer units. This will likely change in the near future since the US Centers for Medicare and Medicaid recently granted current procedural

terminology (CPT) codes which allow reimbursement for RCM in the United States (Rajadhyaksha et al. 2016). In the meantime, several authors have described scenarios in which RCM may be more useful. In 2016, Borsari et al. performed a prospective study in which they evaluated 1279 equivocal lesions with RCM and suggested that RCM may be more useful in lesions located on the head and neck, lesions harboring dermoscopic regression, and lesions located on severely sun-damaged skin (Borsari et al. 2016). In addition, multiple publications have suggested that RCM works best in featureless, amelanotic, or pink lesions, especially those located on the face, since it is capable of identifying small amounts of melanin (Braga et al. 2009; Edwards et al. 2016; Fraga-Braghiroli et al. 2014; Guitera et al. 2016). Another situation where RCM is of particular interest is as a complement of digital dermoscopic monitoring in patients harboring atypical mole syndrome. In these patients with multiple moles, when a change occurs, RCM can help determine whether a lesion is nevus or melanoma, since changes during follow-up have very high sensitivity but lower specificity for melanoma (Carrera and Marghoob 2016; Salerni et al. 2013). This same scenario may be applicable to patients with germline mutations such as *CDKN2A*, *CDK4*, *MITF*, *BAP1*, or carriers of *MC1R* polymorphisms (Carrera and Marghoob 2016). These patients have increased melanoma susceptibility, and subtle clinical changes or new, dermoscopically featureless lesions may actually be melanomas. Obviously, RCM has also an important role when evaluating unusual lesions such as melanoma mimics (i.e., seborrheic keratoses, lichen planus-like keratoses, or pigmented actinic keratoses) or collision tumors (Carrera and Marghoob 2016; Carrera et al. 2017b). Finally, another situation where RCM has proven to be beneficial and also highly cost-effective is in the lesion mapping of lentigo maligna and lentigo maligna melanoma (LM/LMM)(Edwards et al. 2016). This is again due to the fact that RCM can identify small amounts of melanin which is generally scarce in LM/LMM. Hence, RCM and specifically the handheld microscope allows the determination of pre-treatment margins (Champin et al. 2014; Gualdi et al. 2016; Guitera et al. 2013; Hibler et al. 2017; Yélamos et al. 2017), even in the operation room (Hibler et al. 2015), as well as for monitoring after treatment (Alarcon et al. 2014a; Hibler et al. 2017).

Total Body Photography and Digital Dermoscopy

Total body photography (TBP) involves imaging the whole or almost the whole body surface digitally, usually linked to a dermoscopy system that also produces digital dermoscopic images. These systems include software allowing a comparison of images taken at different time points, such as at semiannual skin examinations. These comparisons over time allow the detection of new lesions or changes in pre-existing lesions in atypical mole syndrome patients. This method is used in referral centers and pigmented lesions clinics and can be combined with digital dermoscopy. TBP with new devices at high resolution introduce polarized light and in some cases 3D reconstruction of skin surface (Rayner et al. 2018). Computer-automated algorithms are in development to help detect new lesions and changes in melanocytic lesions during follow-up visits of patients at high risk for melanoma (Esteva et al. 2017; Haenssle et al. 2018; Marchetti et al. 2018).

Sequential digital dermoscopic imaging (SDDI) allows the registration and follow-up of individual atypical or equivocal lesions in patients with atypical moles or many moles. In these patients, changes in size, color, or dermoscopic structures may allow the recognition of early melanoma with a significant reduction in skin biopsies (Salerni et al. 2012b, 2014). This approach can be particularly useful for monitoring patients with multiple atypical nevi that would be impractical to remove in one session (Argenziano and Soyer 2001). Short-term and long-term follow-up are different strategies with a clinical benefit in this indication. The combination of TBP and DD has been shown to improve the detection of early melanoma in high-risk patients with the benefits of both techniques (Salerni et al. 2012b), as well as increased cost-efficiency (Que et al. 2016).

There are several types of changes that can be detected with sequential digital dermoscopic imaging. The first is an increase or decrease in overall pigmentation of the lesion caused by seasonal variation in sun exposure. This kind of change is common and not concerning. A second category of change is enlarging nevi with circumferential brown clods distributed symmetrically around the lesion's periphery. These lesions are more common in people under 20 years old, and are not necessarily melanoma, as evidenced by their symmetrical growth, but do need to be closely monitored for further changes, particularly in adults. A third category of changing melanocytic lesions are those with a pronounced change in dermoscopic architecture, colors, or size, particularly asymmetric changes. These lesions should be treated with caution and considered for excision to rule out a melanoma (Buhl et al. 2012; Salerni et al. 2012a, 2013).

Other Noninvasive Detection Methods

Besides dermoscopy and RCM, electrical impedance spectroscopy (EIS) and MelaFind are two imaging systems that have been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the complementary study of atypical melanocytic lesions in order to detect melanoma.

Electrical impedance spectroscopy (EIS) is a novel nonvisual method employed in skin cancer diagnosis that suggests whether a lesion should be considered benign or malignant based on scores. EIS charts the current that flows between the cells as a series of curves. Tumor cells are characterized by irregular curves due to their polymorphism. From these curves, the system calculates a score that reflects the degree of abnormality of the skin lesions. In a pivotal trial (Malvehy et al. 2014), EIS has proved to achieve a high sensitivity (96.6%) in the detection of early melanoma without fully compromising specificity (34.4%). However, the system is limited to flat melanocytic tumors in non-volar areas and mucosa, and therefore further studies are needed for assessing its role in the diagnosis of other lesions (Welzel and Schuh 2017).

MelaFind acquires multispectral images of lesions in ten bands from 430 nm (blue) to 950 nm (near infrared) and uses automatic image analysis to assess the degree of tissue disorganization and labels lesions as either "not melanoma" or "melanoma cannot be ruled out." Highly disorganized lesions are more suspicious for melanoma. A multicenter study of clinically equivocal melanocytic lesions found that the sensitivity of MelaFind for early malignant melanoma was high at >98%, but the specificity was only 9.5%, although this was higher than the specificity of dermatologist readers who assessed clinical images of the lesions (3.7%; $P = 0.02$) (Monheit et al. 2011).

Raman spectroscopy is another optical technique that has been approved by the EMA, but not the FDA. This technique measures the chemical vibrational modes of molecules induced by light in the tissue of interest by assessing color shifts in scattered photons, with an algorithm converting the data into a percentage predicted probability that the lesion is malignant. Current technology has developed to allow the spectrum to be measured in vivo in less than 1 s, with a skin cancer diagnostic specificity of 0.20–0.75 for fixed sensitivity of 0.99–0.90 (Zhao et al. 2017). In the case of melanoma, the authors included a limited number of tumors, and Breslow thickness was not reported (Wang et al. 2015; Zhao et al. 2015, 2016).

OCT is an interferometric procedure, able to detect the intensity of backscattered infrared light from biological tissue by measuring the optical path length (Ulrich et al. 2016). Current OCT devices have a limited resolution compared to RCM, but they have a superior depth of penetration. Different OCT methods include frequency domain OCT (FD-OCT), dynamic OCT (D-OCT), high-definition OCT (HD-OCT), and LC-OCT. FD-OCT is primarily used in the diagnosis of nonpigmented basal cell carcinoma (BCC) and other nonpigmented skin cancers. Although there are some reports on the OCT patterns of melanoma (Cheng et al. 2016; Gambichler et al. 2015a, b), further studies are needed to understand the accuracy of OCT in melanoma diagnosis.

Dermoscopic Features of Melanoma and Melanoma Simulants

Dermoscopy principally allows users to assess whether a lesion is malignant or benign by assessing the presence or absence of common local dermoscopic features (Fig. 2) and global dermoscopic patterns. One difficulty is the multitude of overlapping descriptive and metaphoric terms used to describe such patterns and features, with features being recognized and described by many dermatologists over more than two decades. Descriptive terms have the advantage of being more straightforward, while metaphoric terms have the advantage of being a memorable description of complex structures. Kittler et al. (2016) have recently proposed a standardized dictionary of terms based on a consensus panel of experts, which aims to eliminate redundant terminology and lay a foundation for new features to be given standardized descriptive terms. Each dermoscopic pattern or feature is described as a version of one of five elements (lines, clods, dots, circles, and pseudopods); areas that lack any of these features are called structureless.

Lines describes pigmented lines or streaks, either straight or curved. Dots are very small round structures, not larger than a terminal hair, and multiple dots are generally the same size and shape. Clods are larger than dots, round to oval or angulated, and multiple clods can vary in size and shape. Circles are circles of color, with normal skin or the background color of the lesion inside the circle. Pseudopods are streaks with a knob on the end. Combined with color and spatial arrangement, these elements can be used to describe any dermoscopic structure.

Local Dermoscopic Features

Multiple colors within a lesion are suspicious for melanoma (Fig. 3), while most benign lesions exhibit only one or two colors. The variety of colors in nevi and melanoma are caused by the presence of pigmented melanocytes or melanophages at varying depths in the skin. Black and brown are due to pigment in the epidermis, gray to pigment in the upper dermis, and blue to pigment in the middle dermis (Fig. 4) (Zalaudek et al. 2009).

Pigmented reticular lines are a hallmark of melanocytic lesions, both benign and malignant, with pigmented lines representing elongated rete ridges and meshes representing dermal papillae. Typical reticular lines, found in benign nevus, solar lentigo, lentigo simplex, and dermatofibroma, feature delicate brown lines forming a regular grid over a diffuse light brown background, fading away at the periphery. Thick reticular lines with changes in thickness or multiple colors, also called atypical networks, are highly indicative of melanoma (Fig. 5). They have black, gray, or brown thickened lines, which can appear smudged or out of focus, with irregular meshes. They are often disorganized and distributed irregularly through the lesion, with lines ending abruptly at the edge of the lesion (Kittler et al. 2016; Soyer et al. 2001a; Wolner et al. 2017).

Pigmented lines that are not connected to a network of reticular lines, also called streaks, correspond to junctional nests of melanocytes that form tubules parallel to the skin surface. Generally brown or black, they are of varying size and may or may not converge and include radial segmented lines, also called radial streaming (Fig. 6), and branched lines. They are present at the edges radiating away from the tumor toward normal skin and can form a starburst pattern. Symmetrical, radial lines over a whole lesion are characteristic of a benign Reed nevus and regular streaks are found in other types of benign nevi. However, irregular lines, distributed unevenly through or around the lesion, are strongly indicative of melanoma (Soyer et al. 2001a; Wolner et al. 2017). Importantly, when radial streaming is present symmetrically in an individual older than 12, the lesion should be excised since this can also be a sign of spitzoid melanoma (Lallas et al. 2017).

Pseudopods are pigmented lines with a knob at one end. Similarly to streaks, they correspond to junctional nests of melanocytes that form tubules parallel to the skin surface. Pseudopods are

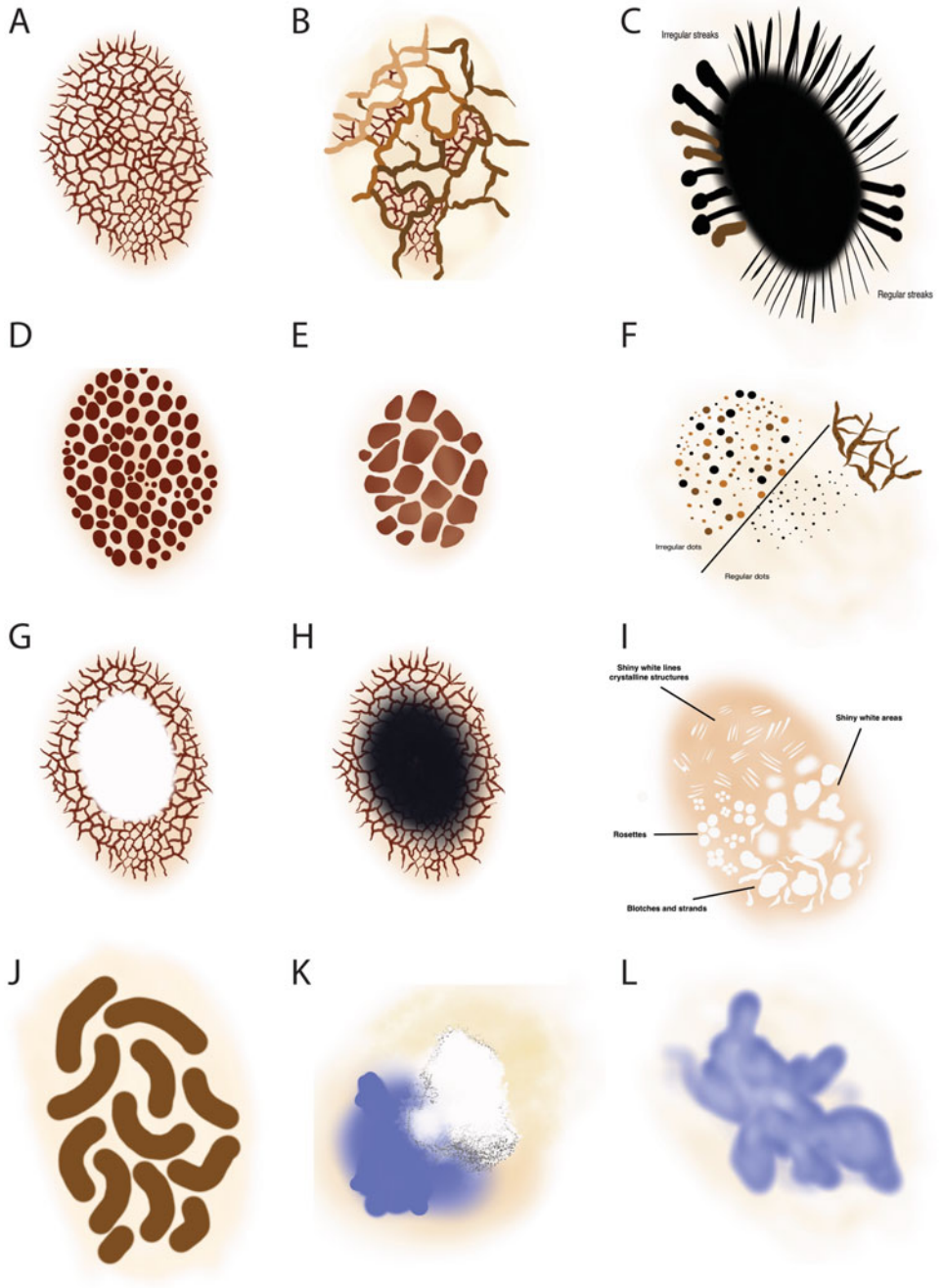

Fig. 2 Common local dermoscopic features. (**a**) Regular reticular lines. (**b**) Reticular lines that vary in color or thickness. (**c**) Streaks and pseudopods. (**d**) Clods. (**e**) Cobblestone clods. (**f**) Dots. (**g**) Hypopigmentation. (**h**) Hyperpigmentation. (**i**) Shiny white lines and other white structures. (**j**) Negative network. (**k**) Regression structures: blue structureless zone, scar-like white structureless zone, and gray dots (peppering). (**l**) Blue-white veil. (Provided by Ralph P. Braun CC BY-NC 4.0)

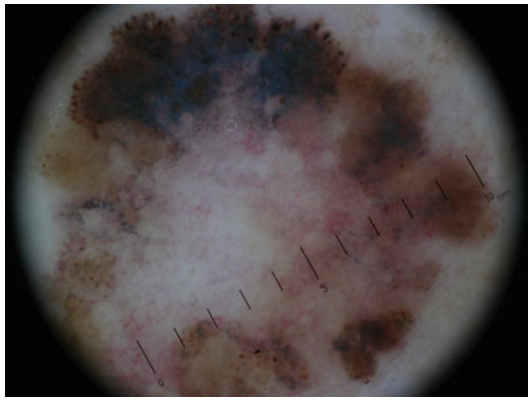

Fig. 3 Multiple colors, including light brown, dark brown, blue, pink, and white, in a melanoma (Breslow thickness 0.9 mm)

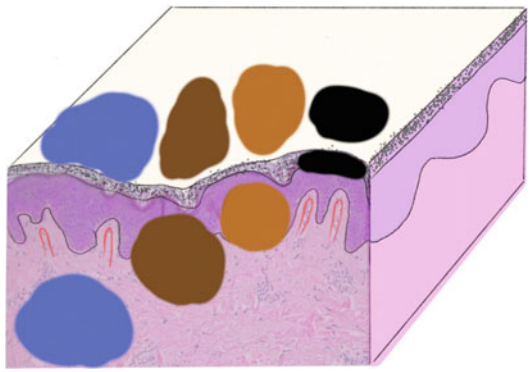

Fig. 4 Lesion color by pigmentation depth. (Provided by Ralph P. Braun CC BY-NC 4.0)

usually arranged circumferentially and symmetrically, also called a starburst pattern, in Reed nevi and melanoma. Asymmetrically arranged pseudopods are indicative of melanoma (Fig. 7) (Kittler et al. 2016; Soyer et al. 2001a). However symmetrically arranged pseudopods cannot exclude melanoma, especially in adulthood.

Shiny white lines, arranged perpendicularly to each other and formerly called crystalline structures, are short, bright lines that only appear under polarized light (Fig. 8). The lines are usually parallel to or at right angles from each other. These structures represent dermal fibroplasia and is associated with invasive melanoma but can also appear in basal cell carcinomas, Spitz nevi, or dermatofibromas (Kittler et al. 2016; Wolner et al. 2017; Yélamos et al. 2018a).

Clods, or globules, are round to oval, sharply demarcated black, gray, or brown structures, representing aggregations of melanocytes, melanophages, or clumps of melanin. The color of the clods corresponds to the location of the aggregations in the layers of the skin. Black structures are focal collections of melanin or melanocytes in the stratum corneum. Brown structures are discrete junctional nests of melanocytes at the dermo-epidermal junction or cap-like pigmentation of melanocytes at the top of the papillary dermis. Gray to blue structures are aggregations of melanocytes or melanophages in the papillary dermis (Yélamos et al. 2018a). In benign nevi, regular clods are distributed evenly through the lesion or in the center of lesion. Irregular clods, unevenly distributed though the lesion, predominantly at the periphery, and of various sizes and shapes, are associated with melanoma (Fig. 9). (Soyer et al. 2001a; Wolner et al. 2017).

Dots are round structures, smaller than clods, and no larger in diameter than a terminal hair. As for clods, the color of dots corresponds to the depth of the pigment in the layers of the skin. In benign nevi, regular dots are distributed evenly through the lesion or in the center of lesion. Irregular dots, unevenly distributed though the lesion but predominantly at the periphery, are associated with melanoma. Gray dots, called peppering or granularity, are a sign of regression and are present in $>10\%$ of melanocytic lesions; they are suggestive of melanoma (Ribero et al. 2016). In addition, a combination of gray dots and gray circles, called annular-granular pattern, is a sign of lentigo maligna (Fig. 10) (Kittler et al. 2016; Soyer et al. 2001a).

Pigmented circles are often a sign of malignancy in facial lesions. Incomplete circles, consisting of asymmetrically pigmented follicular openings, and concentric circles are signs of lentigo maligna (Kittler et al. 2016; Schiffner et al. 2000; Soyer et al. 2001a). These circles sometimes connect with each other and form lines that angulate from each other forming polygonal/rhomboidal structures.

A blue structureless zone can describe a diffuse blue area, usually covering the whole lesion

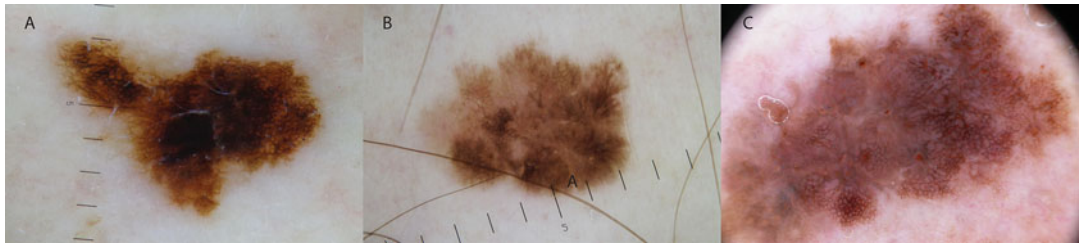

Fig. 5 Irregular or atypical networks. (**a**) Thickened lines in an atypical nevus. (**b**) Lines ending abruptly at the edge of the lesion in a melanoma in situ. (**c**) Smudged or out of focus lines in a melanoma in situ

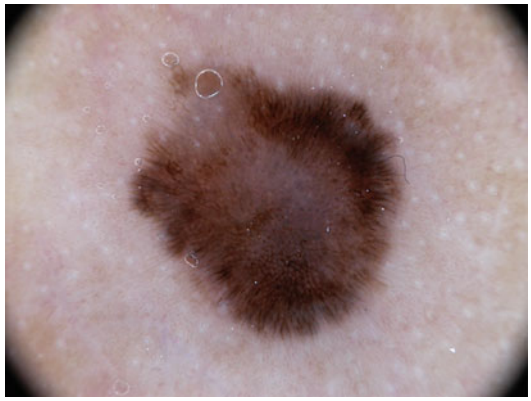

Fig. 6 Radial lines (streaks) distributed irregularly within an atypical Spitz nevus

as found in benign blue nevi, or a blue-white veil (Fig. 11), which is a blue or blue-gray area overlaid by a whitish, ground-glass-like haze, representing heavily pigmented melanocytes in the upper dermis overlaid by an acanthotic epidermis with compact orthokeratosis (Yélamos et al. 2018a). The presence of a blue-white veil over a raised area should raise suspicion for invasive melanoma, and lesions with structureless blue areas that do not cover the whole lesion are suspicious for melanoma. Blue structureless zones are often associated with thick or multicolored reticular lines, dots, clods, or atypical lines, and blue structureless areas are often palpable. Blue structureless areas are commonly found in melanoma and not commonly found in benign Clark nevi, though it can appear in benign Reed or Spitz nevi (Soyer et al. 2001a; Wolner et al. 2017).

Brown or black structureless zones, also called blotches (Fig. 12), are dark brown to black areas which obscure the visualization of other underlying dermoscopic structures. Blotches represent areas of heavy melanin pigmentation throughout the epidermis or upper dermis or a lamella of pigment in the stratum corneum. Structureless zones can be described as localized, being confined to a small section of the lesion, or diffuse, spreading across most or all of the lesion. Regular structureless zones are symmetrical in shape and are distributed more or less symmetrically throughout the lesion; these suggest a benign lesion. Irregular structureless zones are either asymmetric in shape or are distributed asymmetrically in the lesion, such as a single off-center blotch near the periphery of the lesion or multiple blotches distributed asymmetrically. These irregular zones suggest melanoma. However, areas of structureless, heavy pigmentation are so common in pigmented lesions that their diagnostic significance is limited (Soyer et al. 2001a; Wolner et al. 2017).

Hypopigmented structureless areas in an otherwise normal pigmented lesion represent areas in the epidermis and dermis that have little melanin and can be focal, multifocal, or diffuse (Fig. 13). Various kinds of hypopigmentation are found in benign nevi, and some melanomas display irregularly outlined hypopigmented areas.

Hypopigmented reticular lines around pigmented clods, also called a negative network (Fig. 14), are usually found in melanomas or Spitz/Reed nevi. The clods can be elongated or laid out in a serpiginous fashion (Kittler et al. 2016; Pizzichetta et al. 2013; Soyer et al. 2001a; Wolner et al. 2017).

Scar-like areas are white structureless areas, usually paler than nearby normal skin, and do not have shiny white lines or visible blood vessels (Fig. 15a). Scar-like areas represent areas of regression and

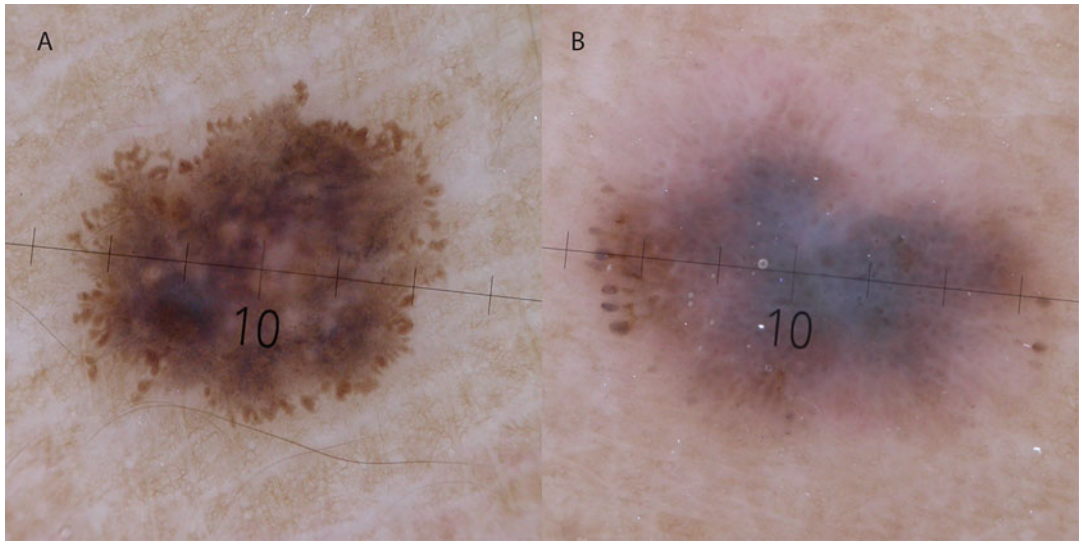

Fig. 7 Pseudopods. (**a**) Regular pseudopods around a growing nevus. (**b**) Pseudopods distributed irregularly at periphery of a melanoma (Breslow thickness 0.3 mm)

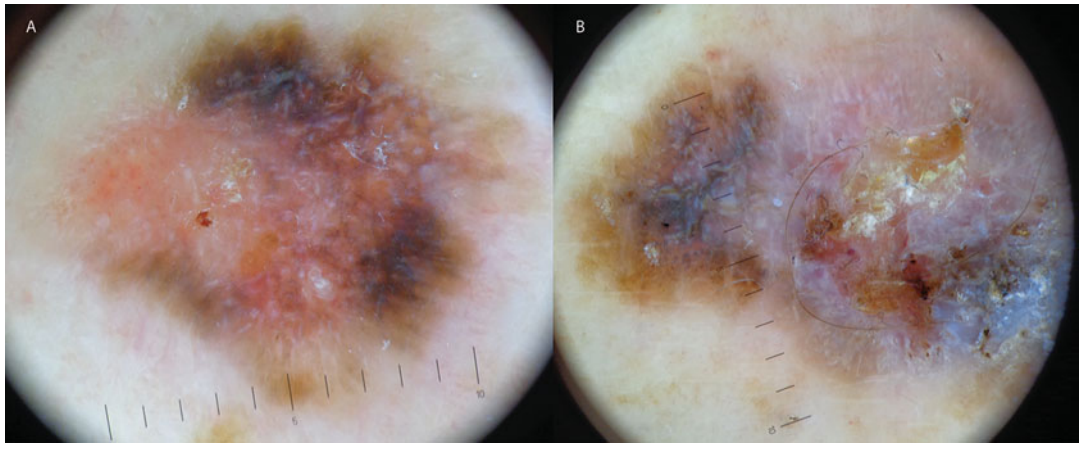

Fig. 8 White lines with perpendicularity (shiny white lines or crystalline structures) in melanomas. (**a**) Breslow thickness 1.6 mm. (**b**) Breslow thickness 1.4 mm

fibrosis. When white and blue areas appear alongside each other, they can be difficult to distinguish from a blue-white veil for novice dermoscopists, but they are usually not palpable while an area of blue-white veil is often palpable (Fig. 15b). While white scar-like areas occasionally appear in benign nevi, they are highly specific for melanomas. One exception is a central white structureless area, usually found in dermatofibromas (Fig. 16) (Soyer et al. 2001a; Wolner et al. 2017).

Vascular structures can also be visible with dermoscopy, if noncontact polarized dermoscopy is used or if contact dermoscopy is performed without pressing too hard or by using ultrasound gel (Figs. 17 and 18). Milky red areas, which are light pink structureless areas with occasional presence of vessels, strongly suggest melanoma. Other vascular structures that suggest melanoma are serpentine vessels (linear with multiple bends, also called linear irregular), helical vessels

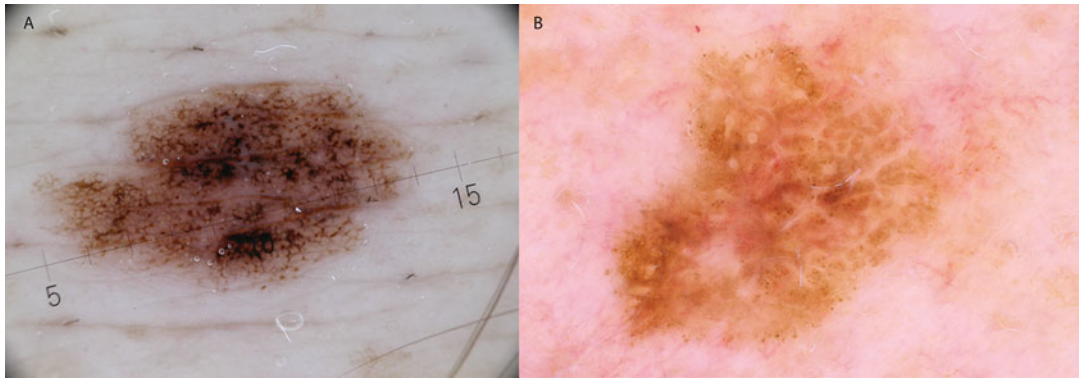

Fig. 9 (**a**) Irregular/asymmetrically distributed clods (globules) in an atypical nevus. (**b**) Asymmetric peripheral dots and clods in a melanoma (Breslow thickness 0.45 mm)

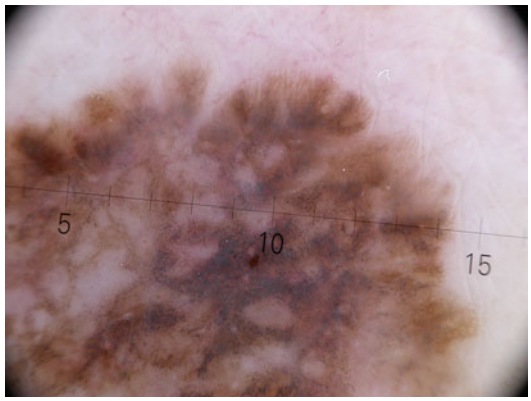

Fig. 10 Gray dots (peppering) in a melanoma (Breslow thickness 0.5 mm)

(vessels twisted into loops along a central axis, also called corkscrew), and polymorphous vessels (more than one type of vascular structure) (Fig. 19). Linear vessels, which are straight or mildly curved, can be a sign of melanoma when they are irregular with different sizes, shapes, and curves and a haphazard or asymmetrical distribution (Braun et al. 2004; Carrera et al. 2016; Kittler et al. 2016; Soyer et al. 2001a; Wolner et al. 2017).

Common Global Dermoscopic Patterns

There are eight common global dermoscopic patterns for melanocytic lesions: reticular, globular, cobblestone, homogenous, starburst, parallel (acral surfaces), unspecific, and multicomponent. When regular, they are usually indicative of a melanocytic nevus, while if they are irregular, unspecific, or multicomponent, they are often associated with melanoma. A uniform, symmetrical, or regularly distributed pattern is usually a sign of a benign nevus, but abnormalities in several of the usually benign patterns are indicative of melanoma. When evaluating acral skin, generally pigment located on the furrows (parallel furrow pattern) is suggestive of a nevus, whereas pigment located on the ridges (parallel ridge pattern) is suggestive of melanoma.

Reticular pattern, also called a pigment network, is a network or grid of brown lines, commonly found in benign acquired melanocytic nevi, solar lentigines, and thin melanomas (Fig. 20). Despite its presence in such a broad range of lesions, alterations in the thickness, color, or uniformity of the lines can indicate a malignant lesion (irregular pigment pattern). Regular, light to dark brown lines that fade toward the periphery of the lesion are typical of a benign nevus, while thickened, gray, brown, or black lines distributed irregularly and ending abruptly at the edge of the lesion are indicative of melanoma. Previously, a facial feature presenting as round meshes corresponding to follicular openings was called a pseudonetwork (Fig. 21) (Soyer et al. 2001a);

Globular pattern consists of numerous small, round to oval brown and black clods, of varying sizes, or dots, no bigger than the diameter of a terminal hair (Kittler et al. 2016). This pattern is

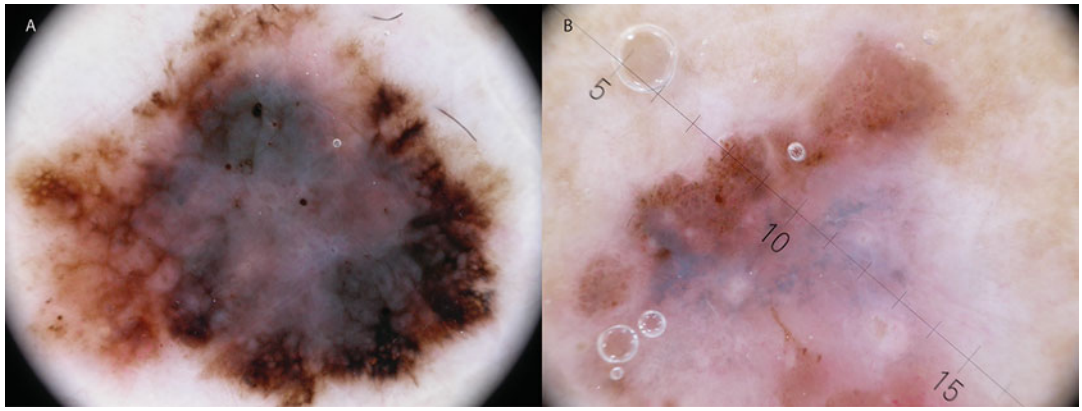

Fig. 11 Blue-white veil in melanomas. (**a**) Breslow thickness 1.4 mm. (**b**) Breslow thickness 0.7 mm

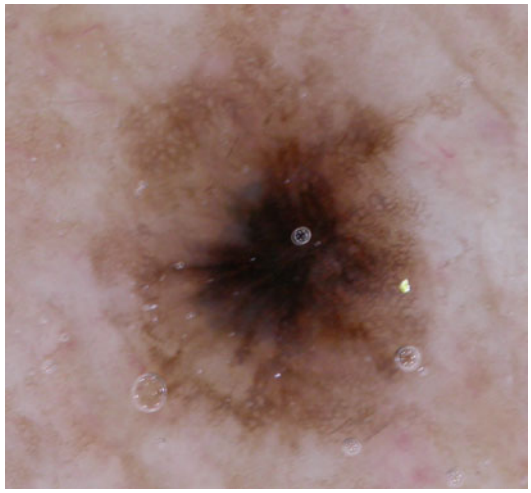

Fig. 12 Structureless black zone (blotch/lamella) at the center of a nevus

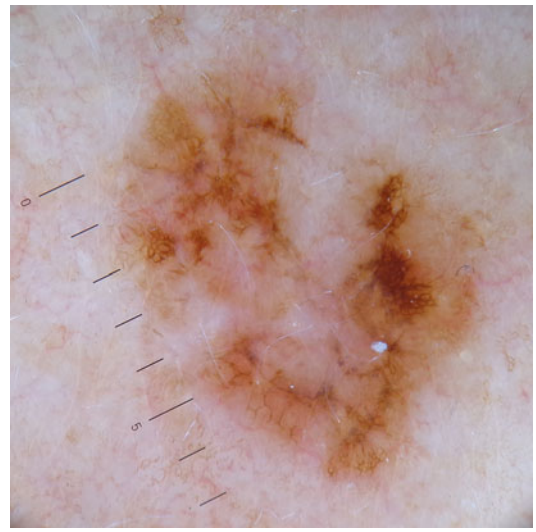

Fig. 13 Multifocal hypopigmentation in an atypical nevus

also common in benign nevi and can appear in combination with reticular lines (Soyer et al. 2001a). Circumferential brown clods, a rim of small clods around the edge of a lesion, indicate a growing melanocytic lesion (Fig. 22).

Cobblestone pattern consists of large polygonal clods packed closely together, resembling cobblestones (Fig. 23). This pattern is common in benign nevi such as papillomatous dermal nevi or congenital nevi (Soyer et al. 2001a).

Homogenous pattern is characterized by a structureless zone of diffuse brown, pink, black, or blue pigmentation in the absence of other structures. It is common in a variety of lesions, such as blue nevi, BAP1-inactivated melanocytic tumors, and nodular or metastatic melanomas (Fig. 24) (Soyer et al. 2001a; Yélamos et al. 2018c).

Starburst pattern consists of circumferential pseudopods or circumferential radial streaks arranged symmetrically around the perimeter of the lesion (Fig. 25). It is characteristic of benign Spitz/Reed nevi but can also appear in spitzoid melanomas (Lallas et al. 2017; Soyer et al. 2001a).

Parallel furrow patterns are thin parallel lines of pigment on the acral surfaces of the feet or

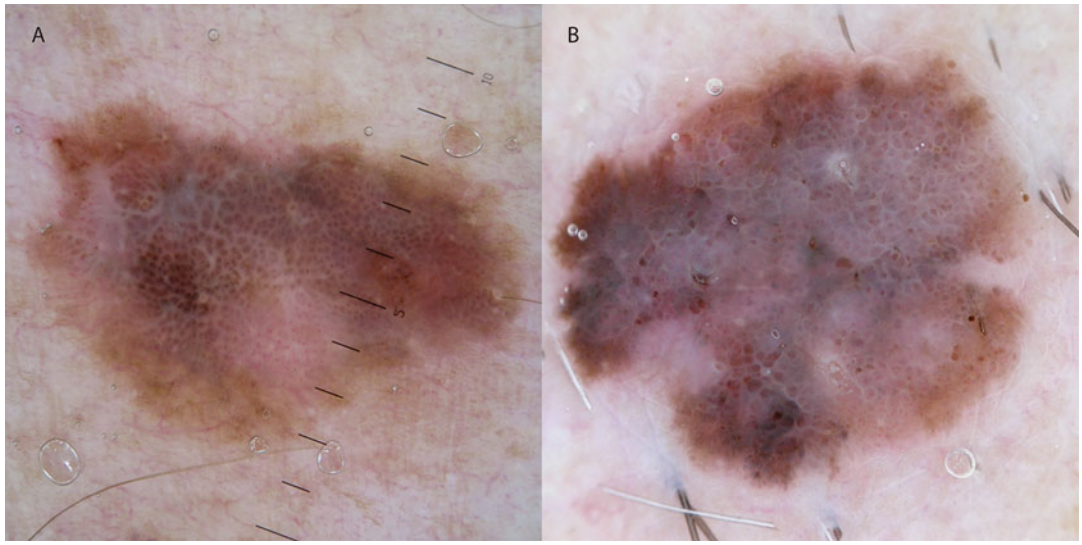

Fig. 14 Hypopigmented reticular lines around brown clods (negative network) in melanomas. (**a**) Breslow thickness 0.6 mm. (**b**) Breslow thickness 0.7 mm

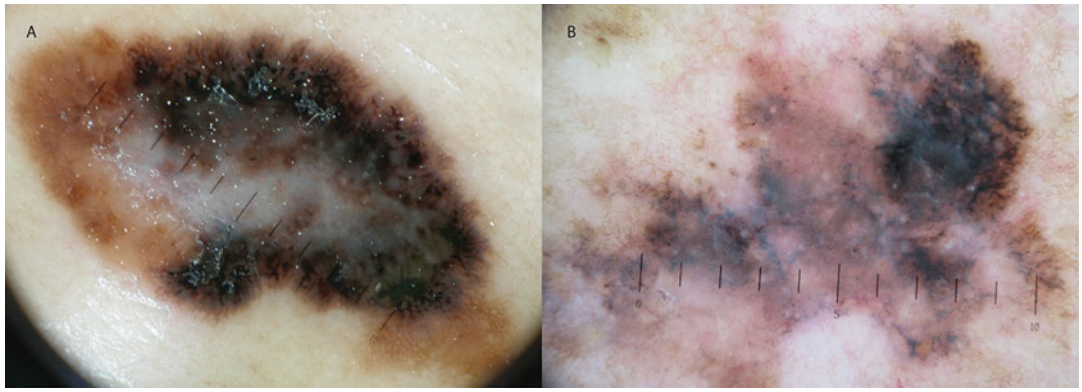

Fig. 15 Regression structures. (**a**) Central, irregularly shaped white structureless area (scar-like area) in a melanoma. (**b**) Blue-gray structureless zones in a melanoma (Breslow thickness 0.3 mm)

hands, arranged along the cristae or sulci, or more rarely at right angles to them (Fig. 26). Thin lines of pigment in the furrows are common in acral nevi, but thick lines of pigment on the ridges are more suggestive of melanoma (Soyer et al. 2001a).

Unspecific lesions have none of the above patterns and are often but not always associated with melanoma (Soyer et al. 2001a).

Many lesions have a multicomponent or complex pattern, consisting of three or more distinctive dermoscopic patterns within the same lesion (Fig. 27). For example, a lesion with a cluster of clods, a zone of reticular lines, and a structureless zone of pigment would be considered multicomponent. This pattern is often found in melanoma and basal cell carcinoma and less frequently in benign nevi (Soyer et al. 2001a).

Global dermoscopic patterns are influenced by a number of patient-specific factors that may mislead dermoscopists. Benign nevi can change with age: in children, globular or structureless patterns are common, and during adolescence, symmetrically growing nevi with circumferential brown clods are

common, while in adults, reticular lines are the most common pattern. Nevi are also prone to change during pregnancy, with reversible changes in color, thickness of reticular lines, new clods, or more prominent vasculature. Exposure to UV can also cause reversible changes in size, the darkness of pigment, erythema, and the development of irregular clods or thickened lines. Skin type influences pigment distribution in nevi, with type I skin tending to light brown nevi with central hypopigmentation, types II and III light to dark brown with multifocal pigmentation, and type IV to dark brown nevi with central hyperpigmentation. Finally, even benign nevi in melanoma patients are more likely to have mixed dermoscopic pattern, such as reticular-globular or globular-structureless, than more uniform nevi (Zalaudek et al. 2009).

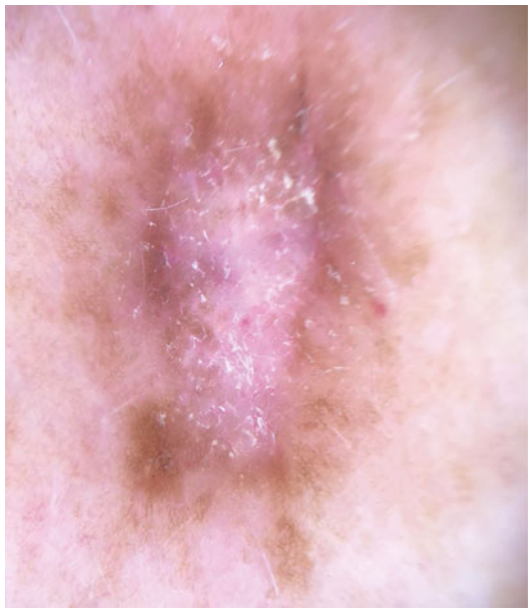

Fig. 16 Central white structureless zone in a dermatofibroma

Anatomical Site Considerations

Site-specific anatomical structures influence dermoscopic features in the trunk and extremities, face, palms and soles, nails, and mucosal surfaces, in turn influencing the dermoscopic presentation of in situ and early invasive melanoma (Breslow index <0.76 mm). Intermediate and thick melanomas (Breslow index >0.75 mm) have usually destroyed the site-specific anatomic structures of the skin, so dermoscopic features of these melanomas are usually independent of the anatomic location (Soyer et al. 2001b).

On the trunk, arms, legs, and dorsal surfaces of the hands and feet, more than 70% of melanomas have a multicomponent pattern or reticular lines that are thick or varied in color (atypical pigment network). Irregular forms of dots, clods, radial

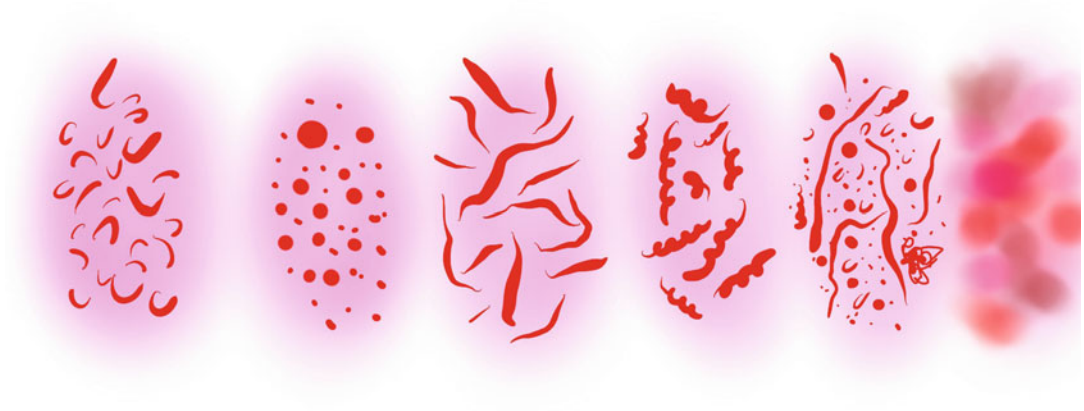

Fig. 17 Vascular structures visible with dermoscopy. (**a**) Curved (comma-like). (**b**) Dotted. (**c**) Serpentine (linear irregular). (**d**) Helical (corkscrew). (**e**) Polymorphous. (**f**) Pink structureless clods (milky red globules). (Provided by Ralph P. Braun CC BY-NC 4.0)

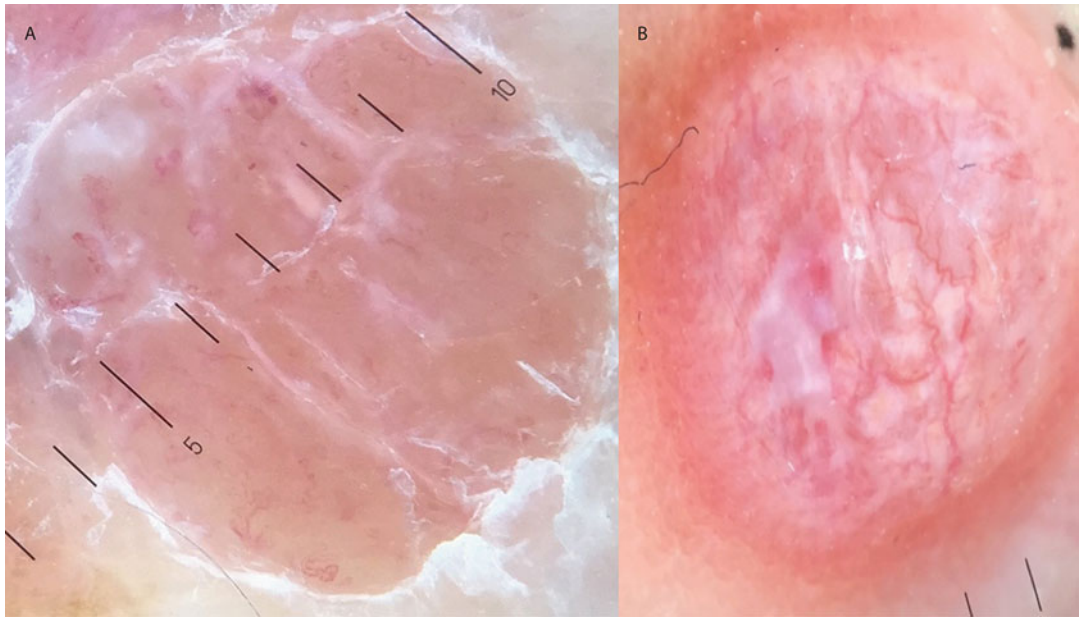

Fig. 18 Vascular structures suggestive of melanoma. (**a**) Milky red area in a melanoma (Breslow thickness 1.3 mm). (**b**) Serpentine vessels, here shown in a mucoid cyst, are common in melanoma

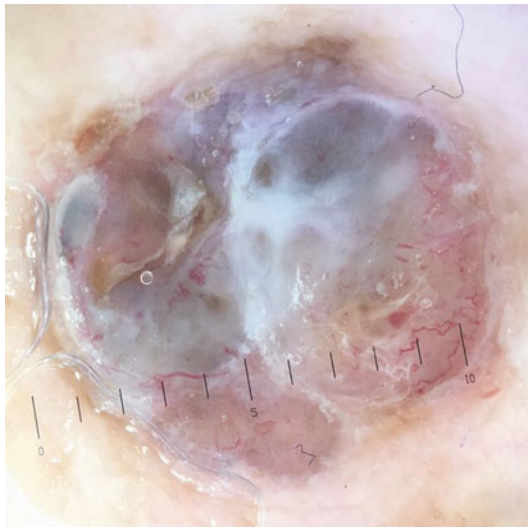

Fig. 19 Polymorphous vessels, where a lesion displays several types of vascular structures, are suggestive of malignancy. Here a basal cell carcinoma includes linear, serpentine, curved, and coiled vessels

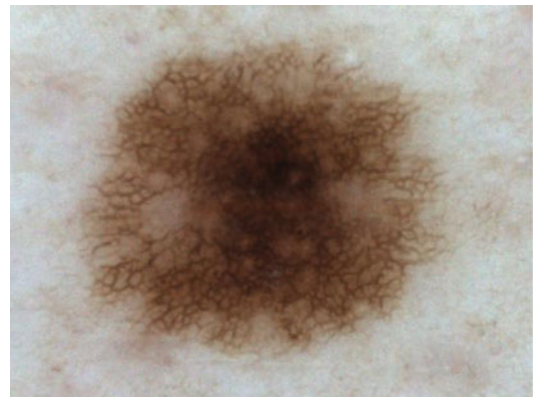

Fig. 20 Regular reticular or network pattern in a nevus, featuring reticular lines of similar color and thickness, fading toward the periphery of the lesion

lines, or structureless zones appear in 50–70% of melanomas, as do regression structures. Blue and white structureless zones (blue-white veil and scar-like depigmentation) are not common features on the trunk and extremities, but do occur in up to 30% of melanomas (Soyer et al. 2001b).

On the face, irregular dots and clods occur in 30–50% of melanomas, as does irregular brown or black structureless zones after the very early stage of melanoma. A brown structureless area interrupted by follicular openings (pseudonetwork) is always present in early invasive facial

melanomas. It is usually atypical, appearing as gray dots and circles (annular-granular structures), gray structureless zones, or angulated or polygonal lines (rhomboid structures). Gray or blue-gray dots and circles around the follicular openings appear in 50–70% of early facial melanomas. Gray structureless zones are formed by the confluence of gray dots and circles around the follicular openings, and angulated or polygonal lines are gray-brown pigment in lines with obvious angles around the follicular openings. These appear in 50–70% of facial melanomas. Concentric pigmented circles appearing within the follicles, gray circles within the follicles, and asymmetric or incomplete circles of pigment around the follicular opening can also indicate melanoma. As the melanoma progresses, structureless zones that obliterate the follicles can also appear (Soyer et al. 2001b; Wolner et al. 2017).

Fig. 21 Structureless zone interrupted by follicular openings (pseudonetwork pattern) in a facial nevus

On the acral surfaces, a thick parallel line on the ridges (parallel ridge pattern), as opposed to thin parallel lines in the furrows (parallel furrow pattern), is a very common feature, appearing in over 70% of melanomas. Here the pigmentation follows the cristae superficiales rather than the sulci superficiales, which is a common sign of benign acral nevi. Irregular forms of dots, clods, and radial lines also appear in 50–70% of melanomas on the acral surfaces. Blue structureless zones (blue-white veil) is an uncommon feature of acral melanomas but does occur in up to 30% of cases. Subcorneal hemorrhage can appear as a clinically concerning jet-black macule, but

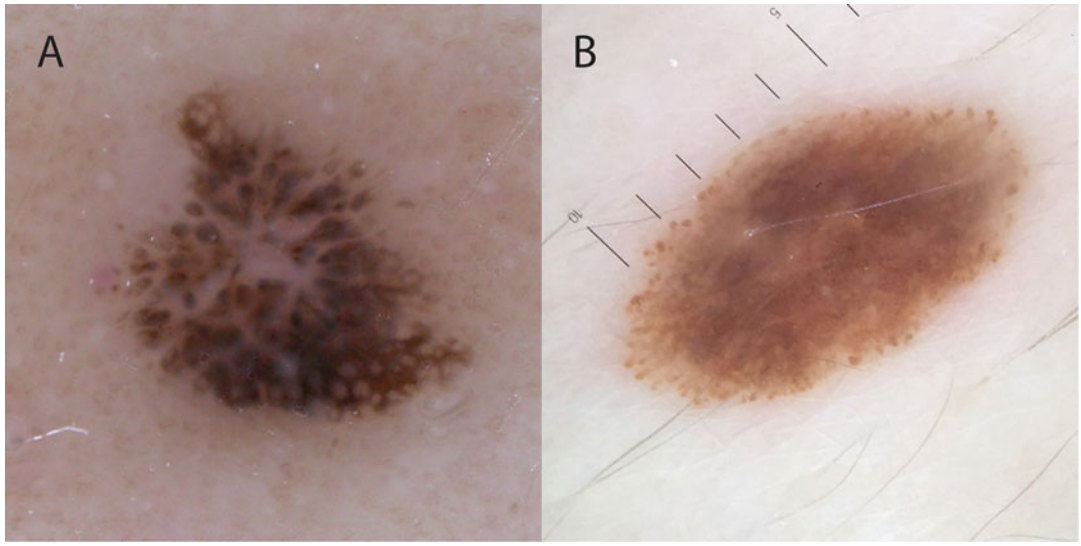

Fig. 22 Globular pattern. (**a**) Central brown clods (globules) in a nevus. (**b**) Circumferential clods (peripheral rim of globules) in a growing nevus

dermoscopic examination usually reveals reddish pigmentation surrounded by small reddish dots (Soyer et al. 2001b).

Melanoma of the nail apparatus appears dermoscopically as multiple brown and black lines, with irregular thickness and arrangement. There may also be interruptions in the pigment bands, and bands are sometimes not parallel (Wolner et al. 2017). Benign nevi of the nail apparatus usually feature a regular band-like pattern, with parallel bands (Zalaudek et al. 2009). Hemorrhage under the nails may present as a clinically concerning round to oval, sharply circumscribed black area. Dermoscopically, these are distinguished from melanomas by dark red or red-black pigmentation surrounded by small reddish dots that are not visible clinically (Soyer et al. 2001b).

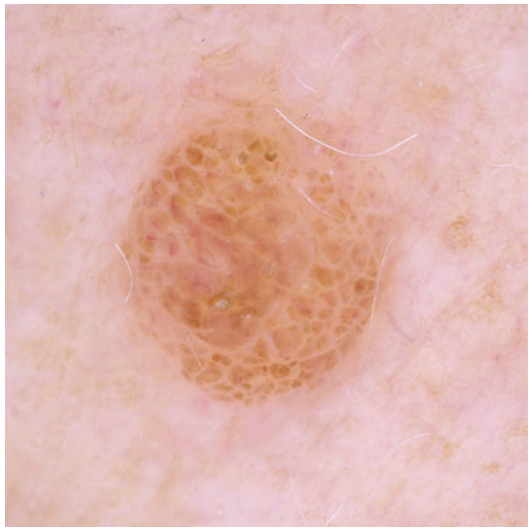

Fig. 23 Cobblestone version

Melanoma of the mucosal surfaces, incorporating the lips, mouth, nasal cavity, and anal and genital surfaces, features structureless zones and gray color in the early stages, progressing to multiple colors and patterns, particularly blue, white, or gray (Wolner et al. 2017). Benign nevi here usually have a globular mixed pattern (Zalaudek et al. 2009), and benign melanoses usually have a pattern of parallel linear or curvilinear brown streaks over a diffuse pigmentation. Benign melanosis sometimes shares features of melanoma, which can only be ruled out by histopathological analysis (Soyer et al. 2001b).

Once a melanoma has progressed to an intermediate or thick stage, anatomic-specific features are less evident. In melanomas with a Breslow index of >0.75 mm, regardless of anatomical site, blue structureless zones are a very common feature, appearing in more than 70% of these thicker melanomas. Irregular forms of dots, clods, radial lines, and structureless zones are

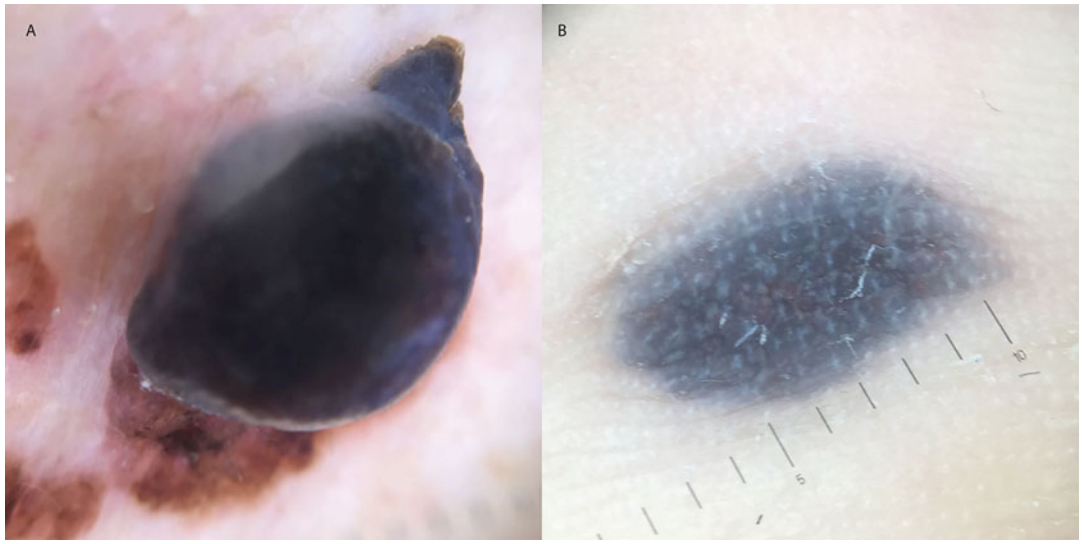

Fig. 24 Homogenous pattern. (**a**) Blue-black homogenous pattern in a melanoma (Breslow thickness 3.7 mm). (**b**) Blue homogenous pattern in a plantar nevus

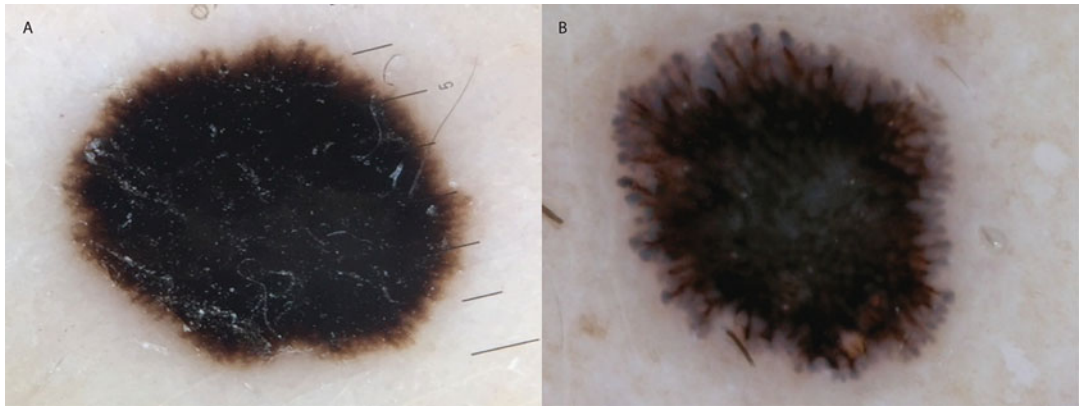

Fig. 25 Starburst pattern. (**a**) With radial lines (streaks) in an atypical Spitz/Reed nevus. (**b**) With pseudopods in a Spitz/Reed nevus

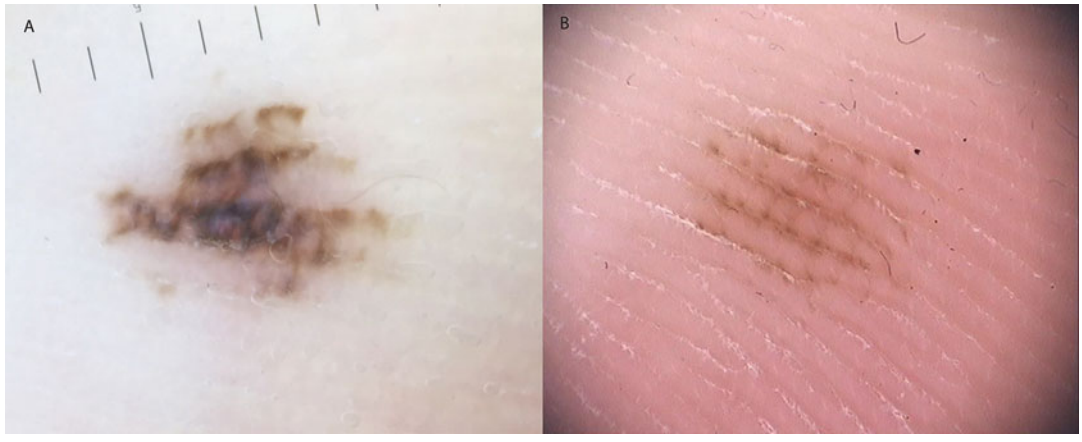

Fig. 26 Parallel furrow pattern of thin parallel lines in the furrows of acral nevi

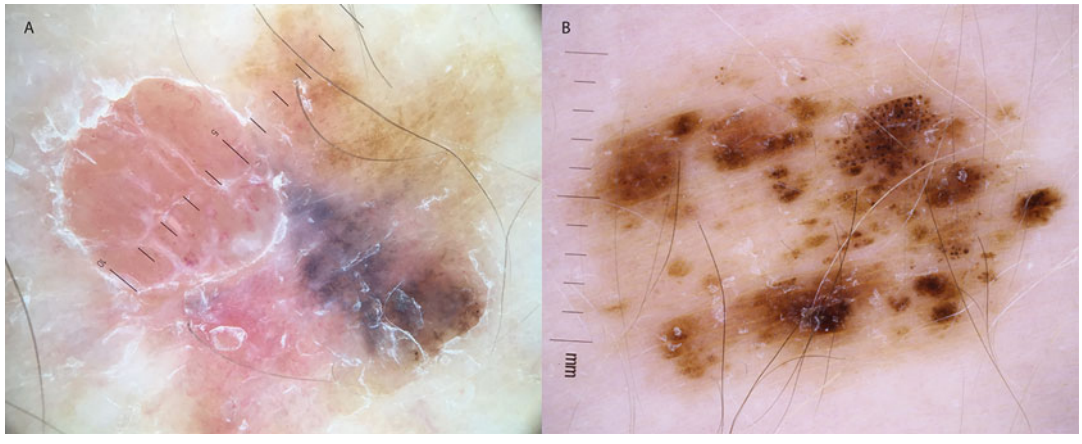

Fig. 27 Multicomponent pattern in (**a**) a melanoma (Breslow thickness 1.3 mm) and (**b**) a nevus

also found in 50–70% of these melanomas, and thick or multicolored reticular lines (atypical pigment networks) or polymorphous vascular patterns are found in 30–50%. Blue-gray structures and white structureless zones (regression structures) are less common but still appear in up to 30% of intermediate and thick melanomas (Soyer et al. 2001b).

Featureless Melanomas

Although most melanomas display at least some degree of asymmetry of pattern, color, and structure, a subset of early melanomas are featureless. Most of these early melanomas can be correctly identified by observing their growth dynamics or detecting an increased or atypical vasculature.

Diagnostic Algorithms for Dermoscopy

While initially only well-trained dermatologists were able to gain increased sensitivity and specificity with dermoscopy (Kittler et al. 2002), the development of the two-step algorithm and other checklists to detect malignancy has enabled primary care physicians to effectively use dermoscopes with a brief online training course (Zalaudek et al. 2006) (see Table 1). However, the more complex method of pattern analysis remains the preferred method of experienced dermoscopists. See Table 2 for a comparison of the sensitivity and specificity of scoring methods.

Two-Step Algorithm

The two-step algorithm first classifies the lesion as melanocytic or non-melanocytic (Fig. 28). Pigmented features that indicate a melanocytic lesion are reticular lines on non-glabrous skin, brown to black dots or clods, radial lines, homogeneous blue zones, or parallel lines of pigment on the acral surfaces. In the absence of pigmented features, users look for specific criteria that can identify the lesion as non-melanocytic.

Features indicating a non-melanocytic lesion are curved, parallel thin brown lines (fingerprint-like structures); curved thick lines (cerebriform patterns); radial lines connected to a common base (leaflike structures); white dots or clods (milia-like cysts); brown, yellow, or black clods (comedo-like openings); irregular blue-gray clods or structureless zones; large clustered blue clods (blue-gray ovoid shapes); concentric clods (spoke wheel-like areas); branched (arborizing) vessels; red-blue clods (lacunae); red-blue to red-black structureless zones; and ulceration.

Featureless lesions that do not show any melanocytic or non-melanocytic lesion structures require special attention. Because it is not uncommon to encounter amelanotic and hypomelanotic melanomas that are structureless, all so-called featureless lesions should be viewed with extreme suspicion, and assessed alongside melanocytic lesions, especially if the lesion exhibits irregular linear or dotted blood vessels, both of which are commonly seen in melanoma (Argenziano et al. 2003; Soyer et al. 2001b).

The second step of the two-step algorithm involves the assessment of melanocytic and featureless lesions with a checklist of dermoscopic features to differentiate benign nevi from melanoma. Pattern analysis is typically used by experienced dermoscopists, while novices in dermoscopy may find one of the score-based algorithms described below useful in assessing melanocytic lesions. A study by the International Dermoscopy Society, where 130 participants scored 477 lesions for the presence or absence of specific dermoscopic features found in various score-based algorithms, found that the Menzies method had the highest sensitivity (95.1%) but the lowest specificity (24.8%); the other algorithms had similar levels of diagnostic accuracy (68.9–77.9%) (Carrera et al. 2016).

Three-Point Checklist

With the three-point checklist, users score the lesion on the presence of three criteria:

Table 1 Diagnostic algorithms and checklists for dermoscopy. These methods apply only after a lesion has been assessed to be melanocytic

Method	Components	Scoring	Formula and interpretation
Three-point checklist[a]	1. Asymmetry in color or structure	1	2 or more is indicative of a melanoma or BCC
	2. Irregular reticular lines with thickened lines and irregular holes	1	
	3. Blue or white pigmentation	1	
ABCD or ABCD-EFG rule[b, c]	Asymmetry: in 0, 1, or 2 axes, in contours, color, or structure	0–2	(A score × 1.3) + (B score × 0.1) + (C score × 0.5) + (D score × 0.5) < 4.75 = benign nevus 4.75–5.45 = suspicious for melanoma >5.45 = melanoma
	Border: abrupt cutoff of pigment pattern at the periphery in 0–8 sectors	0–8	
	Colors: presence of up to six colors (white, red, light or dark brown, blue-gray, black)	1–6	
	Dermoscopic structures: presence of reticular lines, structureless zones, branched lines, dots, or clods	1–5	
	For nodular melanomas: elevated, firm, and growing for at least 1 month		
Menzies scoring[d]	Negative features		Lesions with both of these features are not melanomas
	1. Symmetry of pattern: symmetry of pattern across all axes through the center of the lesion; symmetry of shape is not required		
	2. Single color: black, gray, blue, dark brown, tan, or red		
	Positive features		Lesions with one or more of these features are suspicious for melanoma
	1. Blue structureless zone (blue-white veil): irregular structureless area of confluent blue pigmentation with an overlying white "ground-glass" haze, not occupying the whole lesion or associated with red-blue clods		
	2. Multiple brown dots: focal areas of dots, not clods		
	3. Pseudopods: bulbous, often kinked projections at the edge of the lesion, connected to the lesion body or pigment network and not distributed regularly or symmetrically around the lesion		
	4. Radial segmental lines (radial streaming): finger-like extensions at the edge of the lesion, not distributed regularly or symmetrically around the lesion		
	5. White structureless zone (scar-like depigmentation): areas of white, distinct, irregular extensions, not confused with areas of hypopigmentation or depigmentation caused by simple loss of melanin		
	6. Peripheral black dots or clods: found at or near the edge of the lesion		
	7. Five to six colors: gray, black, blue, dark brown, tan, or red; white is not scored as a color		
	8. Multiple blue or gray dots: foci of multiple blue or gray dots, not clods, often described as "pepper-like"		
	9. Thick reticular lines: network made of irregular thick "cords," often seen focally thicker		

(*continued*)

Table 1 (continued)

Method	Components	Scoring	Formula and interpretation
Revised seven-point checklist[e]	1. Reticular lines that are thick or that vary in color: a combination of two or more types of pigment network, for example, with different colors or line thickness, distributed asymmetrically within the lesion	1	≥1 = excision recommended
	2. Blue structureless zone (blue-white veil): an area of irregular, confluent structureless blue pigmentation with an overlying whitish area resembling a "ground-glass" film; the pigmentation must not occupy the whole lesion	1	
	3. Atypical vascular pattern: serpentine or dotted vessels or pink structureless areas, not clearly combined with regression structures	1	
	4. Irregular radial lines (streaks): more than three brown or black bulbous or finger-like projections, not clearly combined with a pigment network and asymmetrically distributed around the edge of the lesion	1	
	5. Irregular structureless zones (blotches): structureless brown or gray areas distributed asymmetrically within the lesion	1	
	6. Irregular dots/clods: more than three dots or clods, black or brown, distributed asymmetrically within the lesion	1	
	7. Regression structures: scar-like white structureless zones or blue pepper-like dots (granules)	1	
CASH scoring system[f]	Color:	1 point for each color	<8 = likely benign ≥8 = suspicious for melanoma
	Light brown		
	Dark brown		
	Red		
	Black		
	White		
	Blue		
	Architectural disorder:		
	None/mild	0	
	Moderate	1	
	Marked	2	
	Symmetry in shape and dermoscopic structures:		
	Biaxial symmetry	0	
	Monoaxial symmetry	1	
	Biaxial asymmetry	2	
	Homogeneity/heterogeneity based on number of dermoscopic structures:	1 point for each type of structure	
	Dot/clods		
	Radial lines (streaks)/pseudopods		
	Blue structureless zone (blue-white veil)		
	Regression structures: white or blue structureless zones or blue or gray dots and circles		
	Irregular dark structureless zones (blotches)		
	Polymorphous blood vessels		

(*continued*)

Table 1 (continued)

Method	Components	Scoring	Formula and interpretation
Chaos and Clues[g]	Chaos: asymmetry of structure or color		The presence of chaos AND one or more of the clues indicates biopsy
	Absent: no action required		
	Present: assess for clues below		
	Clues:		
	1. Eccentric (asymmetrical) structureless zone; any color except color of nearby normal skin	1	
	2. Thick lines that are reticular or branched	1	
	3. Gray or blue structures	1	
	4. Black dots or clods at the periphery of the lesion	1	
	5. Segmental (asymmetrically distributed) radial lines or pseudopods	1	
	6. White lines, paler than nearby normal skin	1	
	7. Polymorphous vessels	1	
	8. Parallel lines that are on the ridges of acral surfaces or that are chaotic on the nails	1	
TADA[h]	Level 1: Is the lesion an unequivocal example of	Yes – no action No – go to level 2	Lesions with these diagnoses do not require treatment
	1. Angioma?		
	2. Dermatofibroma?		
	3. Seborrheic keratosis?		
	Level 2: does the lesion exhibit either	Yes – biopsy No – go to Level 3	Lesions with these features require biopsy
	1. Disorganization or asymmetric distribution of structures or color?		
	2. Starburst pattern?		
	Level 3: are any of the following features present?	Yes – biopsy No – monitor	Lesions with these features require biopsy Lesions that are disorganized but do not have these features require monitoring
	1. Blue-black or gray color		
	2. White structures		
	3. Negative network		
	4. Ulceration or erosion		
	5. Vessels		

[a]Zalaudek et al. (2006)
[b]Chamberlain et al. (2003)
[c]Nachbar et al. (1994)
[d]Menzies et al. (1996)
[e]Argenziano et al. (2011a)
[f]Henning et al. (2007)
[g]Rosendahl et al. (2012)
[h]Rogers et al. (2016)

1. Asymmetry in color or structure, but not in shape
2. Thick reticular lines (atypical network) with irregular holes
3. Blue or white structures in the lesion

The presence of more than one of these characteristics is suggestive of melanoma or basal cell carcinoma. Zalaudek et al. (2006) studied 150 participants who were trained to use the three-point checklist with an online training set of 15 dermoscopic images and then tested on a set of 150 dermoscopic images of histopathologically confirmed benign lesions, melanomas, and basal cell carcinomas. The majority of the participants were dermatologists, but general physicians, medical students, and other skin healthcare professionals were also represented. Users of all levels of

experience had a sensitivity for melanomas and basal cell carcinomas of between 88.9% and 92.7% and a specificity ranging between 59.8% and 74.5%, with specificity improving with longer dermoscopy experience (Zalaudek et al. 2006).

Table 2 Comparison of dermoscopic scoring systems (Carrera et al. 2016; TADA was not assessed in this study)

Scoring system	Sensitivity % (95% CI)	Specificity % (95% CI)
Three-point checklist	68.9 (59.8–77.1)	58.7 (53.4–63.8)
ABCD rule	74.8 (66.0–82.3)	59.4 (54.0–64.6)
Menzies method	95.1 (89.0–98.4)	24.8 (20.1–30.1)
Seven-point checklist	70.6 (61.5–78.6)	57.5 (52.2–62.7)
CASH score	77.9 (69.7–85.1)	50.9 (45.4–56.4)
Chaos and Clues	82.4 (66.1–96.5)	40.2 (35.1–45.5)

Revised Seven-Point Checklist

Users score the lesion on the presence of seven criteria. These are the presence of:

1. Reticular lines that appear to be a combination of two or more different colors or line thicknesses, distributed asymmetrically within the lesion (atypical network).
2. Blue-white veil, an irregular, confluent blue structureless zone with an overlying area of whitish "ground-glass" film; the blue zone must not occupy the whole lesion.
3. An atypical vascular pattern, such as irregularly linear or dotted vessels or milky red areas that are not clearly combined with regression structures.
4. More than three irregular radial lines, seen as brown or black bulbous or finger-like projections, not clearly combined with a network of

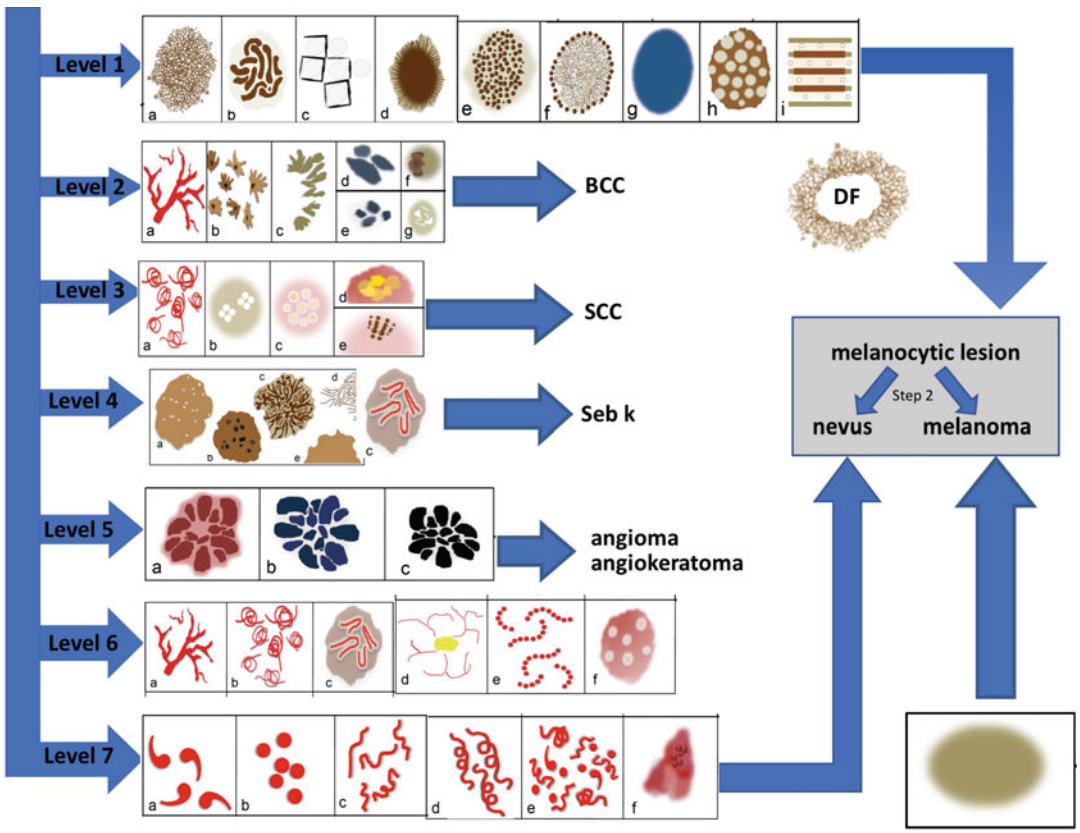

Fig. 28 Schematic of the two-step algorithm workflow. (Provided by Ralph P. Braun CC BY-NC 4.0)

reticular lines and asymmetrically distributed around the edge of the lesion.
5. Irregular structureless zones of brown or gray pigmentation distributed asymmetrically within the lesion.
6. More than three dots or clods, black or brown, distributed asymmetrically within the lesion.
7. Regression structures, including white structureless zones (scar-like depigmentation), or gray dots (peppering).

Each criterion present scores 1 point; lesions scoring one or more points are considered to be potential melanomas. The original seven-point checklist, dividing the criteria into major (2 points each) and minor criteria (1 point each), was based on lesions that were either obvious melanomas or clinically equivocal lesions already warranting excision (Argenziano et al. 1998); the revised checklist was tested on a wider range of lesions including lesions earmarked for monitoring rather than excision. In a study of 300 lesions, the revised seven-point checklist had a sensitivity of 87.8% and specificity of 74.5% (Argenziano et al. 2011a).

ABCD Rule of Dermoscopy and Clinical EFG Rule

The ABCD rule scores the lesion on the presence of four differently weighted dermoscopic features:

(A) Asymmetry in contours, color, or structure; absent (0 point), along one axis (1 point), or along two axes (2 points)
(B) Border with an abrupt cutoff of pigment at the lesion periphery
(C) Colors in the lesion, up to six (white, red, light brown, dark brown, blue-gray, or black)
(D) Dermoscopic structures of reticular lines, structureless zones, radial lines, dot, or clods

After bisecting the lesion with two axes at right angles to each other, arranged for maximum symmetry, asymmetry is scored as being absent (0 point), along one axis (1 point), or along two axes (2 points). Abrupt border cutoff is assessed by diving the lesion periphery into eight even sectors; an abrupt border in any section is 1 point, up to a total of 8 points if present in all sectors. Colors present in the lesion are awarded 1 point each for white (lighter than the surrounding normal skin), red, light brown, dark brown, blue-gray, or black, up to a total of 6 points. The dermoscopic structures present are scored 1 point each for reticular lines, structureless zones (when larger than 10% of the lesion), radial lines (when at least two are present), dots (when at least two are present), or clods, up to a total of 5 points. The final score is calculated by:

$$(A\ \text{score} \times 1.3) + (B\ \text{score} \times 0.1) + (C\ \text{score} \times 0.5) + (D\ \text{score} \times 0.5)$$

A score of less than 4.75 indicates a benign lesion. A score of 4.75–5.45 is suspicious for melanoma, and over 5.45 is highly suspicious for melanoma. In a prospective study of 172 melanocytic lesions, the ABCD rule had a sensitivity of 90% and a specificity of 93% (Nachbar et al. 1994). However, the ABCD rule is not suitable for detecting melanoma on the acral surfaces and mucosal surfaces (Soyer et al. 2001b).

To better detect nodular melanomas, which often do not display the traditional ABCD criteria, EFG criteria have also been added:

(E) Elevated
(F) Firm
(G) Growing

These EFG criteria become concerning when they are present for at least 1 month to rule out temporary inflammatory lesions such as acne or insect bites (Chamberlain et al. 2003).

Menzies Method

Menzies scoring assesses lesions on the presence of two negative and nine positive features. Negative features are:

1. Symmetry of pattern, across all axes through the center of lesion; symmetry of shape is not required.

2. Single color across the whole lesion: black, gray, blue, dark brown, tan, or red.

Lesions with both these negative features are not melanoma.

Positive features are:

1. Blue-white veil, consisting of a confluent, irregular, blue structureless zone overlaid with a white or ground-glass-like haze that does not cover the whole lesion and is not associated with red-blue clods (lacunae)
2. Focal areas of multiple brown dots; does not include clods
3. Circumferential pseudopods, including bulbous or kinked projections from the lesion body or from reticular lines that are not distributed symmetrically around the whole lesion
4. Segmental radial lines (also called radial streaming), consisting of finger-like extensions at the edge of the lesion that are not distributed symmetrically around the lesion
5. White structureless zones (scar-like depigmentation), consisting of distinct areas of white with irregular extensions that are not simply areas of hypopigmentation
6. Black dots or clods at the periphery of the lesion
7. Presence of five or six colors, including gray, black, blue, dark brown, tan, or red, but not including white
8. Foci of blue or gray dots, often described as pepper-like; does not include clods
9. Thick reticular lines with irregular thick "cords," often focally thicker

Lesions with one or more of the positive features are suspicious for melanoma. A study of 164 lesions assessed by 130 dermoscopists found that this method had a sensitivity of 92% and a specificity of 71% (Menzies et al. 1996).

CASH Acronym

The CASH acronym stands for Color, Architectural disorder, Symmetry, and Homogeneity/Heterogeneity.

C) Number of colors in the lesion: light brown, dark brown, red, black, white, and blue (1 point each)
A) Architectural disorder of the lesion rated as mild (0 point), moderate (1 point), or marked (2 points)
S) Symmetry in shape and dermoscopic structure, assessed as biaxial symmetry (0 point), monoaxial symmetry (1 point), or biaxial asymmetry (2 points)
H) Homogeneity or heterogeneity of dermoscopic structures in the lesion: dots/clods, radial lines/pseudopods, blue structureless zones, gray dots/white structureless zones (regression structures), other pigmented structureless zones, and polymorphous blood vessels (1 point for each type of structure)

The overall score is the sum of the scores for each category. Lesions with a score of less than 8 are likely benign, and lesions with a score of eight or higher are suspicious for melanoma. A study of 325 lesions found a sensitivity of 98% and specificity of 68% for this method (Henning et al. 2007).

Chaos and Clues

The Chaos and Clues algorithm emphasizes the often chaotic nature of malignant growths and outlines several dermoscopic clues indicating malignancy.

Chaos: is asymmetry of structure or color present? If no, the lesions need no intervention. If yes, assess the lesion for clues of malignancy.

Clues: unless the lesion is an unequivocal seborrheic keratosis, biopsy is indicated if one or more of the following clues are present:

1. Eccentric structureless area, any color except the color of nearby normal skin
2. Thick lines that are reticular or branched
3. Gray or blue structures
4. Black dots or clods at the periphery
5. Segmental (asymmetrically distributed) radial lines or pseudopods
6. White lines, paler than nearby normal skin
7. Polymorphous vessels

8. Parallel lines along the ridges on acral surfaces or chaotic parallel lines on the nails

Chaos and Clues was designed for use by Australian primary care physicians, who manage half of all skin cancers in Australia, for the diagnosis of melanomas, pigmented SCCs, and pigmented BCCs. In a study of 463 consecutively treated lesions, it had a sensitivity of 90.6% and specificity of 62.7% for skin malignancies of any type (Rosendahl et al. 2012).

TADA

Triage Amalgamated Dermoscopic Algorithm (TADA) was developed for use with polarized light dermoscopy and aims to detect organized or symmetrical malignant lesions, such as spitzoid melanoma, as well as the more common disorganized, asymmetrical melanomas. However, it does require users to already be able to recognize and exclude some common benign lesions. Users work through three levels of the algorithm in a stepwise manner.

Level 1. Is the lesion an unequivocal

1. Angioma
2. Dermatofibroma
3. Seborrheic keratosis

If yes, the lesion requires no action. If no, proceed to Level 2.

Level 2. Does the lesion exhibit

1. Architectural disorder, including asymmetric distribution of colors or structures
2. Starburst pattern

If yes, the lesion should be biopsied. If no, proceed to Level 3.

Level 3. Are any of the following features present?

1. Blue-black or gray color
2. White structures
3. Negative network
4. Ulceration or erosion
5. Vessels

If yes, the lesion should be biopsied. If no, the lesion should be monitored.

An observational study of 120 participants who were given a 1-day training course and then assessed 50 dermoscopic images found that TADA has a sensitivity of 94.8% and specificity of 72.3% for malignant skin lesions (Rogers et al. 2016).

Pattern Analysis

Pattern analysis, first proposed by Pehamberger et al. after a study of 3000 pigmented lesions (Pehamberger et al. 1987), is often preferred by expert dermatologists and is based on a critical, simultaneous assessment of individual dermoscopic criteria to distinguish melanoma, various types of nevi, lentigines, mucosal surface melanoses, pigmented basal cell carcinomas, seborrheic keratoses, vascular lesions, and dermatofibromas (see Table 3). Pattern analysis recognizes that each diagnostic category is characterized by a few global patterns with a distinctive combination of local features, with some additional uncommon features providing additional diagnostic clues and some confounding features that are uncommon within a particular diagnostic category and can lead to false-positive or false-negative diagnoses (Soyer et al. 2001b). Most benign nevi fall into one of the global patterns, as discussed above, and tend to exhibit symmetry of dermoscopic colors and structures. Any lesion that deviates from one of these global benign patterns must be viewed with caution.

Melanoma commonly has a multicomponent pattern and uncommonly a reticular, globular, parallel ridge, or unspecific pattern. Common local features are reticular lines that vary in color or thickness within the same lesion, irregular dots/clods/radial lines, blue structureless zones, irregular brown or black structureless zones, white structureless zones (scar-like depigmentation), gray dots and/or circles, and irregularly distributed dotted or linear vessels. Uncommon local features are looped (hairpin) vessels and hypopigmented structureless zones. Confounding features that sometimes appear in melanoma are a homogenous or starburst pattern, regular reticular lines, regular dots/clods/radial lines, and white

Table 3 Pattern analysis: features of common skin lesions

Lesion type	Global patterns	Common local features	Uncommon features	Confounding features
Melanocytic lesions				
Melanoma	Common: Multicomponent Uncommon: Reticular Globular Parallel ridge Unspecific	Reticular lines that vary in thickness or color Irregular radial lines Irregular dots or clods Blue structureless zones Irregular brown or black structureless zones White structureless zones Gray dots or circles Irregularly distributed dotted or linear vessels	Looped vessels Hypopigmented structureless zones	Homogenous pattern Starburst pattern Regular reticular lines Regular radial lines Regular dots or clods White dots or clods
Acquired melanocytic nevi	Common: Reticular Globular Uncommon: Homogenous	Regular reticular lines Regular dots or clods Regularly distributed structureless zones, including hypopigmented zones	Symmetrical radial lines White structureless zones Gray dots and circles	Multicomponent pattern Reticular lines that vary in thickness or color Irregular radial lines Irregular dots or clods Irregular structureless zones Dotted vessels
Dermal nevi, also known as Unna or Miescher nevi	Common: Globular Cobblestone Uncommon: Reticular Homogenous Unspecific	Regular dots or clods Exophytic papillary structures Structureless zone interrupted by follicular openings Curved vessels	White dots or clods Yellow, brown or black clods	Multicomponent pattern Irregular structureless zones
Spitz/Reed nevi	Common: Starburst Negative network Uncommon: Multicomponent	Regular radial lines Regular structureless zones Blue Structureless zones Regular dots or clods	Dotted vessels Regularly distributed reticular lines	Reticular pattern Reticular lines that vary in thickness or color Irregular radial lines Irregular dots or clods Irregular structureless zones
Blue nevi	Homogenous	Blue structureless zone	Hypopigmented structureless zone	Irregular structureless zones Branched vessels

(*continued*)

Table 3 (continued)

Lesion type	Global patterns	Common local features	Uncommon features	Confounding features
Congenital nevi	Cobblestone Globular Reticular Multicomponent	Regular dots or clods Reticular lines Multifocal hypopigmented structureless zones Regular structureless zones	White dots or clods Yellow, brown, or black clods Exophytic papillary structures	White or blue structureless zones Localized irregular structureless zones Gray dots or circles
Solar/actinic lentigines	Reticular	Reticular lines Structureless zones interrupted by follicular openings Diffuse pigmentation	White dots or clods	Reticular lines that vary in thickness or color Irregular structureless zones
Melanoses (mucosal)	Unspecific Parallel	Regular structureless zones Reticular lines	Regular radial lines	Reticular lines that vary in thickness or color Irregular structureless zones
Non-melanocytic lesions				
Basal cell carcinomas	Unspecific Multicomponent	Radial lines connecting to a common base Irregular blue-gray clods Branched vessels	White dots or clods Looped vessels	Irregular blue-gray structureless zones
Seborrheic keratoses	Unspecific Homogenous Reticular	White dots or clods Yellow, brown, or black clods Exophytic papillary structures Regular structureless zones Looped vessels	Reticular lines Hypopigmented structureless zones Thick, curved lines Yellowish clods	Multicomponent pattern Irregular structureless zones Blue or white structureless zones Gray dots or circles Irregular dots or clods
Vascular lesions	Common: Lacunar Uncommon: Homogenous	Red clods Red-black or red-blue structureless zones	Parallel pattern Regular dots or clods White-yellowish keratotic zones or clods	Multicomponent pattern Irregular dots or clods White structureless zones
Dermatofibromas	Common: Reticular Uncommon: Unspecific multicomponent	Dots in arranged in reticular lines Central white structureless zone	Localized structureless zones Crusting Regular dots or clods Erythema	Irregular white structureless zones

dots or clods (milia-like cysts) (Soyer et al. 2001b).

Acquired melanocytic nevi commonly have a reticular or globular pattern and uncommonly a homogenous pattern. Common local features are regular reticular lines, regular dots or clods, and regularly distributed structureless zones, including hypopigmented zones. Uncommon local features are symmetrical radial lines, white structureless zones, and gray dots and circles (regression structures). Confounding features that sometimes appear in acquired melanocytic nevi are a multicomponent pattern, reticular lines that vary in thickness or color, irregular dots/clods/radial lines, irregular structureless zones, and dotted vessels (Soyer et al. 2001b).

Dermal nevi, also called Unna and Miescher nevi, commonly have a globular or cobblestone pattern and uncommonly a reticular, homogenous or unspecific pattern. Common local features are regular dots/clods, exophytic papillary structures, a structureless zone interrupted by follicular openings, and curved (comma) vessels. Uncommon local features are yellow, brown, or black clods (comedo-like openings) and white dots and clods (milia-like cysts). Confounding features that sometimes appear in dermal nevi are a multicomponent pattern and irregular structureless zones (Soyer et al. 2001b).

Spitz/Reed nevi commonly have a starburst pattern or hypopigmented reticular lines around brown clods (negative network pattern) and uncommonly a multicomponent pattern. Common local features are regular radial lines, regular structureless zones, blue structureless zones (blue-white veil), and regular dots/clods. Uncommon local features are dotted vessels and a regular distribution of reticular lines. Confounding features that sometimes appear in Spitz/Reed nevi are a reticular pattern, reticular lines that vary in thickness or color within the lesion (atypical network), irregular dots/clods/radial lines, and irregular structureless zones (Soyer et al. 2001b).

Blue nevi have a homogenous pattern. The common local feature is a regular blue structureless zone covering the whole lesion, and hypopigmented structureless zones are an uncommon local feature. Confounding features that sometimes appear in blue nevi are irregular structureless zones and branched (arborizing) vessels (Soyer et al. 2001b).

Congenital nevi commonly have a cobblestone, globular, reticular, or multicomponent pattern. Common local features are regular dots/clods, reticular lines, multifocal hypopigmented structureless zones, and regular structureless zones. Uncommon local features are white dots and clods (milia-like cysts); yellow, brown, or black clods (comedo-like openings); and exophytic papillary structures. Confounding features that sometimes appear in congenital nevi are white or blue structureless zones or gray dots and circles (regression structures) and localized irregular structureless zones (Soyer et al. 2001b).

Lentigines commonly have a reticular pattern. Common local features are reticular lines or structureless zones interrupted by follicular openings and diffuse pigmentation. An uncommon feature is white dots or clods (milia-like cysts). Confounding features that sometimes appears in lentigo are reticular lines that vary in color or thickness within the lesion and irregular structureless zones (Soyer et al. 2001b).

Melanoses of mucosal surfaces commonly have an unspecific or parallel pattern. Common local features are regular structureless zones and reticular lines. An uncommon local feature is regular radial lines. Confounding features that sometimes appear in melanosis of the mucosal surface are reticular lines that vary in thickness or color and irregular structureless zones (Soyer et al. 2001b).

Melanomas are often morphologic outliers lacking the symmetry of structure, pattern, and color usually found in benign lesions. The ugly duckling concept of melanoma emphasizes that an “outlier” lesion that stands out as distinctly different from the others should be suspect (Scope et al. 2008). In a study of 205 nevi from 18 patients, 83% of patients had a dominant global dermoscopic pattern, defined as a pattern occurring in more than 40% of their nevi (Scope et al.

2006). Most of these patients also had one or two minor patterns that occurred in 20–39% of nevi. In most patients, 80% or more of their nevi could be grouped into one, two, or three patterns (Scope et al. 2006). A similar study of 829 nevi from 23 patients found that 52% of the patients displayed a dominant dermoscopic pattern in their nevi (Hofmann-Wellenhof et al. 2001).

Reflectance Confocal Microscopy Features of Melanoma

Common Confocal Features of Melanoma

In the epidermis, a major feature of melanoma is roundish or dendritic pagetoid cells, twice the size of surrounding polygonal keratinocytes, with dark eccentric nuclei, bright cytoplasm, and thick, short dendrites (Fig. 29a). These pagetoid cells are not obviously connected to surrounding keratinocytes, so they appear to float. As the melanoma becomes thicker and more invasive, the number of pagetoid cells increases and spreads through all epidermal layers. However, in amelanotic melanomas, cells that are usually bright appear hyporeflective due to the lack of melanin. A broadened honeycomb pattern may also be evident in the epidermis, with bright, enlarged, broadened intracellular spaces forming the honeycomb pattern. Areas of irregularly sized keratinocytes or keratinocytes with irregularly thickened contours, or a generally disarranged epidermal structure with unevenly distributed bright granules and particles, are other confocal features of melanoma (Longo and Pellacani 2016).

At the dermo-epidermal junction, atypical cells with irregular sizes, shapes, or reflectivity are a confocal feature of melanoma (Fig. 29b). These cells can be stellate, round, or oval, occasionally with dendritic structures, and have bright cytoplasm, dark nuclei, and clearly outlined borders. A generally nonuniform pattern at the dermo-epidermal junction is a confocal feature of melanoma, with unevenly distributed, irregularly sized and shaped, non-edged dermal papillae, lacking the usual rim of bright cells. Instead the papillae are separated by a series of large, reflective cells or non-discrete aggregations of melanocytes (Fig. 29d) (Longo and Pellacani 2016).

In the upper dermis, melanoma often features single, atypical cells with well-demarcated bright cytoplasm and a dark nucleus infiltrating the papillae. Another feature is dense and sparse nests of nonhomogeneous cells varying in size, shape, and reflectivity (Fig. 29c). Cerebriform nests are uncommon but highly specific for invasive and nodular melanomas. These hyporeflective, fissured nests are amorphous aggregates of low-reflecting cells with no evident nuclei, granular cytoplasm, and poorly defined borders. Inflammation is often present as bright, plump, irregularly shaped cells with no nucleus and poorly defined borders, often crowding in the papillae. Leukocyte infiltration can be seen as bright spots and particles with hyper-reflective cytoplasm, sometimes with a visible nucleus. Finally, fibrosis featuring coarse collagen structures can be seen as amorphous fibrillary material in reticular web-like structures or bundles gathered into large fasciae (Longo and Pellacani 2016).

Diagnostic Algorithms for Reflectance Confocal Microscopy

Several algorithms have been developed and validated to diagnose melanoma using RCM. For melanomas not of the LM/LMM type, the most commonly used algorithms include the Modena algorithm (Pellacani et al. 2007b) and the Barcelona algorithm (Segura et al. 2009) (Table 4). Both evaluate the presence of select RCM features in order to distinguish nevi from melanoma. Additionally, Guitera et al. (2010) described an algorithm to distinguish LM/LMM from other pigmented facial macules.

Modena Algorithm

In 2007, Pellacani et al. developed a semiquantitative algorithm for RCM evaluation of

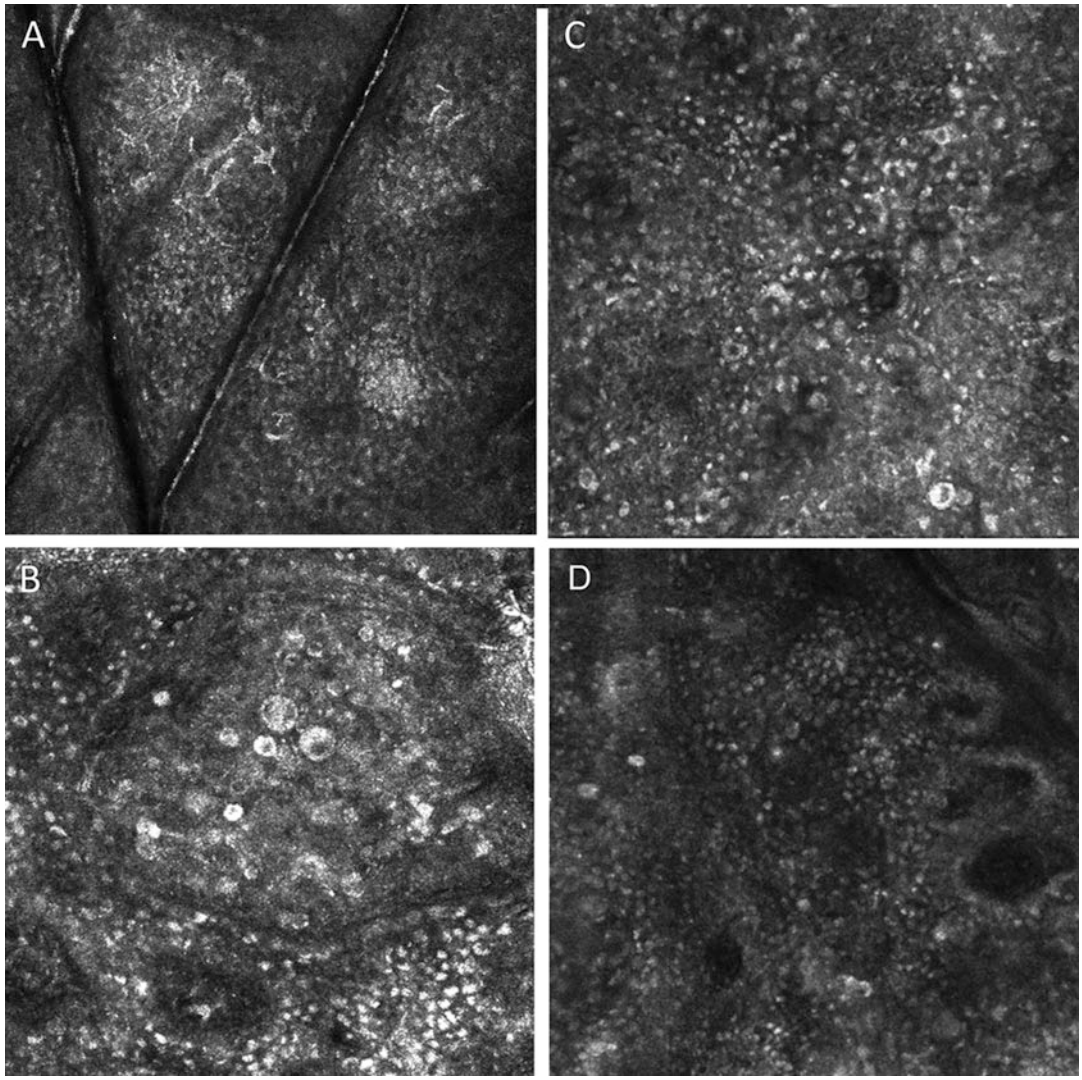

Fig. 29 (**a**) Atypical cells in the epidermis. (**b**) Widespread infiltration at the dermo-epidermal junction. (**c**) Nests with atypical cells. (**d**) Edged and non-edged papillae

melanocytic lesions which includes two major criteria and four minor criteria (Table 4) (Pellacani et al. 2007b). The presence of non-edged papillae and cytologic atypia is a major criterion for the diagnosis of melanoma, and if present add 2 points each to the score. The presence of roundish cells in the superficial layers, pagetoid cells widespread throughout the lesion, cerebriform clusters, and nucleated cells within the dermal papillae are minor criteria, and add 1 point each to the score. According to this algorithm, when a lesion has a score of ≥ 3, the lesion should be excised to exclude a melanoma, with a sensitivity of 91.9% and a specificity of 69.3%.

Barcelona Algorithm

Similarly to the dermoscopic two-step algorithm, the Barcelona algorithm for RCM (Segura et al. 2009) has two steps: the first step allows the reviewer to discriminate whether a lesion is

Table 4 Diagnostic algorithms for RCM

Method	Components	Scoring	Formula and interpretation
Modena algorithm[a]	Major:		Score ≥3 indicates a melanoma
	Non-edged papillae	2	
	Cellular atypia at dermo-epidermal junction	2	
	Minor:		
	Cerebriform nests	1	
	Roundish pagetoid cells	1	
	Widespread pagetoid infiltration	1	
	Nucleated cells in the upper dermis	1	
Barcelona algorithm[b]	**First step: lesion is melanocytic if**		Score ≥ 0 indicates a melanoma
	Dermal papillae present		
	AND at least one of:		
	Cobblestone pattern		
	Pagetoid cells		
	Refractile nests		
	Second step (for melanocytic lesions):		
	Risk features		
	Pagetoid roundish cells in the superficial epidermis	+1	
	Atypical nucleated cells in papillary dermis	+1	
	Protective features		
	Typical basal cells	−1	
	Edged papillae	−1	

[a]Pellacani et al. (2007b)
[b]Segura et al. (2009)

melanocytic or not, and the second step assesses the risk of the lesion being a melanoma. The features included in the Barcelona algorithm are summarized in Table 4. Using a cutoff score of −1 or greater, this algorithm has 100% sensitivity and 57.1% specificity for melanoma. With a cutoff score of ≥0, this algorithm has 86.1% sensitivity and 95.3% specificity for melanoma.

Dermoscopic and Confocal Features of Non-superficial Spreading Melanoma Subtypes

The majority of melanomas, 66% (Chamberlain et al. 2002), are of the superficial spreading subtype, characterized by single or nests of malignant melanocytes that spread vertically into the epidermis and radially at the dermo-epidermal junction, with an in situ component that extends three or more rete ridges beyond the invasive component (Malvehy and Puig 2007). The dermoscopic and confocal diagnostic criteria described above are generally based on the characteristic appearance of this subtype. However, the less common subtypes, nodular melanoma, lentigo maligna melanoma, spitzoid melanoma, and desmoplastic melanoma, also have distinctive dermoscopic and confocal features suggestive of melanoma and are described below.

Nodular Melanoma

Nodular melanoma (NM) accounts for 10–15% of all cutaneous melanomas but is responsible for more than 40% of melanoma deaths (Chamberlain et al. 2002; Mar et al. 2013; Murray et al. 2005). NM is characterized by a rapid growth, and its invasion rate is estimated to be about 0.5–1 mm per month (Liu et al. 2006); 40–50% of NM will have a tumor thickness of >2 mm at diagnosis (Kalkhoran et al. 2010). Histologically, NM is characterized by vertical growth without evidence of an associated radial growth beyond the width of three rete ridges beyond the invasive component

(Clark et al. 1969). Because its epidemiological and morphological features differ significantly from other forms of melanoma, some postulate that NM may originate in the dermis and only gives rise to clinically recognizable features on the skin when it gains enough tumor volume (Zalaudek et al. 2008). A high level of suspicion is required to recognize early forms of NM; thus, any clinically equivocal growing nodule should always be immediately excised (Moscarella et al. 2017).

Fast growing NM more commonly affects men aged >50 years who lack known melanoma risk factors such as multiple nevi, freckles, or signs of sun damage (Chamberlain et al. 2002; Lipsker et al. 2007; Murray et al. 2005), and people with the highest risk for NM are consistently underrepresented during skin cancer screening programs (Hubner et al. 2017). The majority of tumors develop rapidly on previously unaffected skin and are mainly patient detected (Halpern et al. 2014), with patients reporting the tumor "suddenly appearing" or "bulging out" of healthy skin (Chamberlain et al. 2003; Warycha et al. 2008).

Clinically, NM usually appears as a symmetric, red to pink or gray-blue/black plaque or nodule with a diameter <6 mm (Argenziano et al. 2012; Kalkhoran et al. 2010; Pizzichetta et al. 2015). NM often resembles benign lesions such as intradermal nevi, seborrheic keratosis, or hemangiomas (Carrera and Marghoob 2016; Carrera et al. 2017a). They are not detected with the usual algorithms that emphasize asymmetry, the presence of multiple colors, and a diameter >6 mm, so the EFG rule and CCC rule have been developed to aid clinical diagnosis of NM. The EFG rule stands for Elevation, Firmness on palpation, and continuous Growth for more than 1 month (Kelly et al. 2003), while the CCC rule stands for Color (uniform red to blue or black), Contour (roundish), and Change (rapid growth) (Moynihan 1994).

Dermoscopic Features of Nodular Melanoma

Dermoscopy of pigmented NM often features blue and black colors, with a combination of structureless blue areas and black dots, clods, or structureless areas covering at least 10% of the lesion surface. This blue-black rule enhances the discrimination of NM from other benign nodular tumors, such as angiokeratoma, blue nevus, seborrheic keratosis, or hemangioma (Argenziano et al. 2011b). Although blue color is seen in many benign lesions, the combination with black dots and structureless areas is rarely present in benign lesions. Black color may be predictive for a high risk of ulceration (Longo et al. 2013b). For changing heavily pigmented skin lesions, the blue-black rule represents a highly effective clue for the diagnosis of pigmented NM (Fig. 30).

Nonpigmented and hypopigmented NM are also common (Fig. 31) (Pizzichetta et al. 2017). In the case of amelanotic or hypomelanotic NM (AHNM), diagnosis relies on vascular patterns (Zalaudek et al. 2010). While a true amelanotic melanoma lacks any pigmentation, AHNM is characterized by residual or light pigmentation (Menzies et al. 2008). The presence of brown, gray, or blue pigment, especially when seen on the base of a pink nodule, raises the suspicion of melanoma. In the case of amelanotic melanoma, pink structureless zones (milky red areas), short perpendicular white lines (white shiny streaks; only seen under polarized dermoscopy), and a polymorphous vascular pattern are the only diagnostic clues (Pizzichetta et al. 2017; Zalaudek et al. 2010). The most frequent combination of vessel types in melanoma is dotted, linear, and coiled. In contrast to basal cell carcinoma or well-differentiated squamous cell carcinoma, which is characterized by larger vessels, NM more frequently exhibits microvessels of small diameter and length. Pink clods (milky red globules) often show a central serpentine (linear irregular) or helical (corkscrew) vessel, which probably represents neo-angiogenesis (Zalaudek et al. 2010). Thin AHNM is more difficult to diagnose than thick AHNM, because in thin tumors, vascular polymorphism is less evident (Menzies et al. 2008; Pizzichetta et al. 2017; Zalaudek et al. 2010). Short, perpendicular white lines (also known as

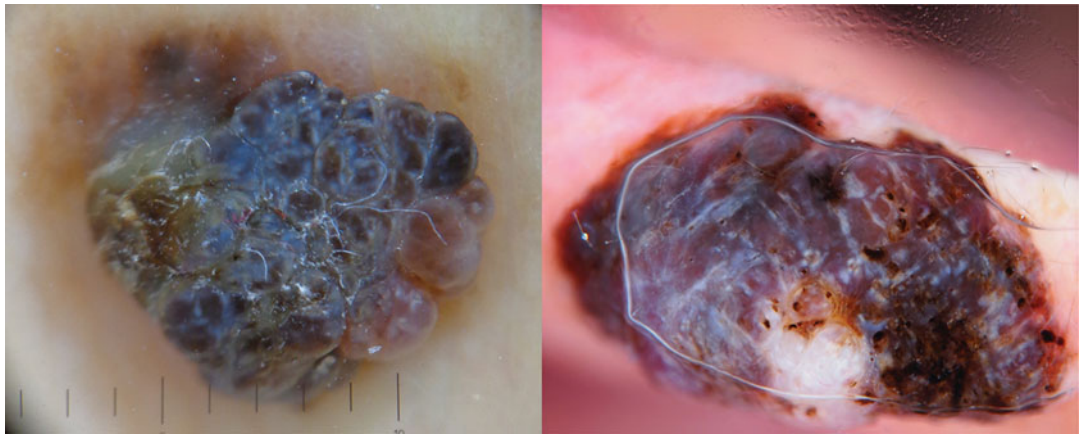

Fig. 30 Blue-black rule in nodular melanomas

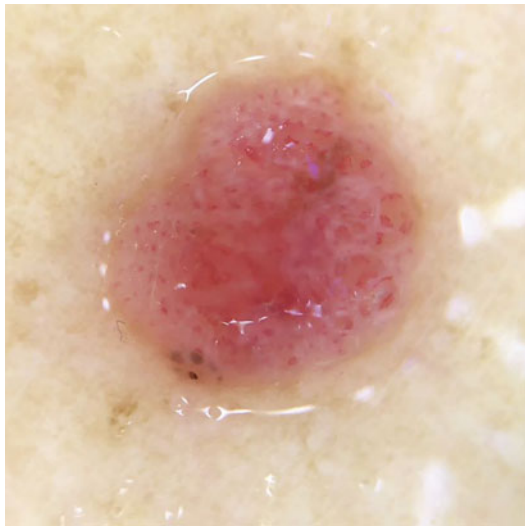

Fig. 31 This hypomelanotic nodular melanoma features polymorphous vessels, pink structureless zones, and small pigmented structures at its base (7 o'clock)

shiny white lines, white thick lines, chrysalis or crystalline structures) are seen only under polarized light dermoscopy but represent an important criterion for diagnosis, especially when associated with polymorphic vessels or pink areas (Di Stefani et al. 2010). Although perpendicular white lines are not very specific for the diagnosis of NM, they are rarely seen in benign skin tumors (Navarrete-Dechent et al. 2016).

Even with these dermoscopic features in mind, NM may be missed. For this reason, specific management rules have been introduced, combining clinical and dermoscopic criteria (Lallas et al. 2013). Any nodular lesion that cannot be confidently diagnosed as benign requires immediate excision. Dermoscopic follow-up of a doubtful nodular lesion is strongly discouraged, because the rapid vertical growth of NM means any delay can worsen prognosis (Moscarella et al. 2017). In particular, pink lesions without a clear clinical and dermoscopic diagnosis should be treated with caution (Moscarella et al. 2017).

Other nodular lesions that should always be excised are those with polymorphous vessels and any ulcerated nonpigmented nodule (Fig. 32) (Moscarella et al. 2017; Zalaudek et al. 2010). Suspected pyogenic granuloma may also require excision as it has overlapping clinical and dermoscopic features with nodular melanoma and can often only be distinguished with histopathology. Destructive methods such laser therapy and/or liquid nitrogen are strongly discouraged as they destroy tissue without the possibility of a histopathological examination.

Reflectance Confocal Microscopy Features of Nodular Melanoma

RCM has significantly improved the early diagnosis of NM. NM usually lacks some of the confocal features of superficial spreading melanoma,

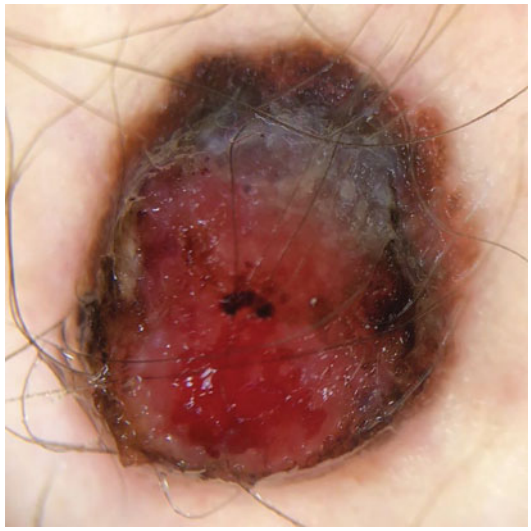

Fig. 32 Ulcerated nodules, such as this pigmented ulcerated nodular melanoma, are highly suspicious for malignancy

such as epidermal disarrangement and pagetoid spreading, but has characteristic confocal features of its own (Fig. 33). In NM, massive proliferation in the dermis obliterates the typical papillary architecture, thus effacing the normal DEJ contours with no visible dermal papillae (Waddell et al. 2018). The basal layer and upper dermis show pleomorphic cells with bright cytoplasm and dark nuclei, while amorphous, hyporeflective nests, called cerebriform nests, are found in the deeper dermis (Segura et al. 2008). Cerebriform nests are very specific for NM although they are not always identified (Guitera et al. 2012; Pellacani et al. 2005). The dermoscopic blue-black rule has also been correlated with confocal features in NM (Longo et al. 2013a). Dermoscopic black color is associated with two different patterns: large black structureless areas (blotches) and irregular black dots/clods. Black structureless areas correspond to large, confluent areas of upwardly migrating melanocyte nests and pagetoid cells in the epidermis, whereas black dots/clods correspond to separate areas of upwardly migrating nests and pagetoid cells. Black color results not only from epidermal melanin or hemoglobin (in the case of ulceration) but also from a dense dermal proliferation of pigmented melanocytes under a significantly thinned but not ulcerated epidermis. Accordingly, black color may be even predictive of ulceration, which is a known negative prognostic criterion. The dermoscopic criterion of perpendicular white lines (shiny white streaks) appears to correlate to dermal fibrosis or collagen bundles under RCM (Pellacani et al. 2007a; Segura et al. 2008). Other RCM features relatively common in NM include the presence of enlarged deep vessels, which dermoscopically correspond to polymorphous vessels, and the presence of plump bright cells in the dermis which correspond to peppering on dermoscopy and to melanophages in histology (Segura et al. 2008; Waddell et al. 2018).

Lentigo Maligna and Lentigo Maligna Melanoma

Lentigo maligna (LM) is an in situ melanoma and lentigo maligna melanoma (LMM) an invasive melanoma, typically found on chronically sun-exposed skin. LM/LMM appears mostly on the head and neck after the fourth decade of life, as a slow-growing asymmetrical macule with irregular borders. It is difficult to differentiate, even dermoscopically, from solar lentigo and early seborrheic keratosis, since all three types of lesions can present with typical melanoma features of multiple colors, asymmetry, irregular borders, and large size. Clinically it can also mimic a melanocytic nevus, lichen planus-like keratosis, and pigmented actinic keratosis (Lallas et al. 2014; Tanaka et al. 2011). Diagnosis is also more difficult because LM/LMM typically lack most classical dermoscopic signs of melanoma, due to the unusual structure of skin on the face with a matrix of hair and sweat follicles and flattened dermo-epidermal junction and rete ridges (Stolz et al. 2002).

Dermoscopic Features of Lentigo Maligna and Lentigo Maligna Melanoma

The Schiffner progression model for LM/LMM describes the evolution of dermoscopic features with the increasing spread of melanoma cells (Fig. 34). The early signs of slate-gray dots,

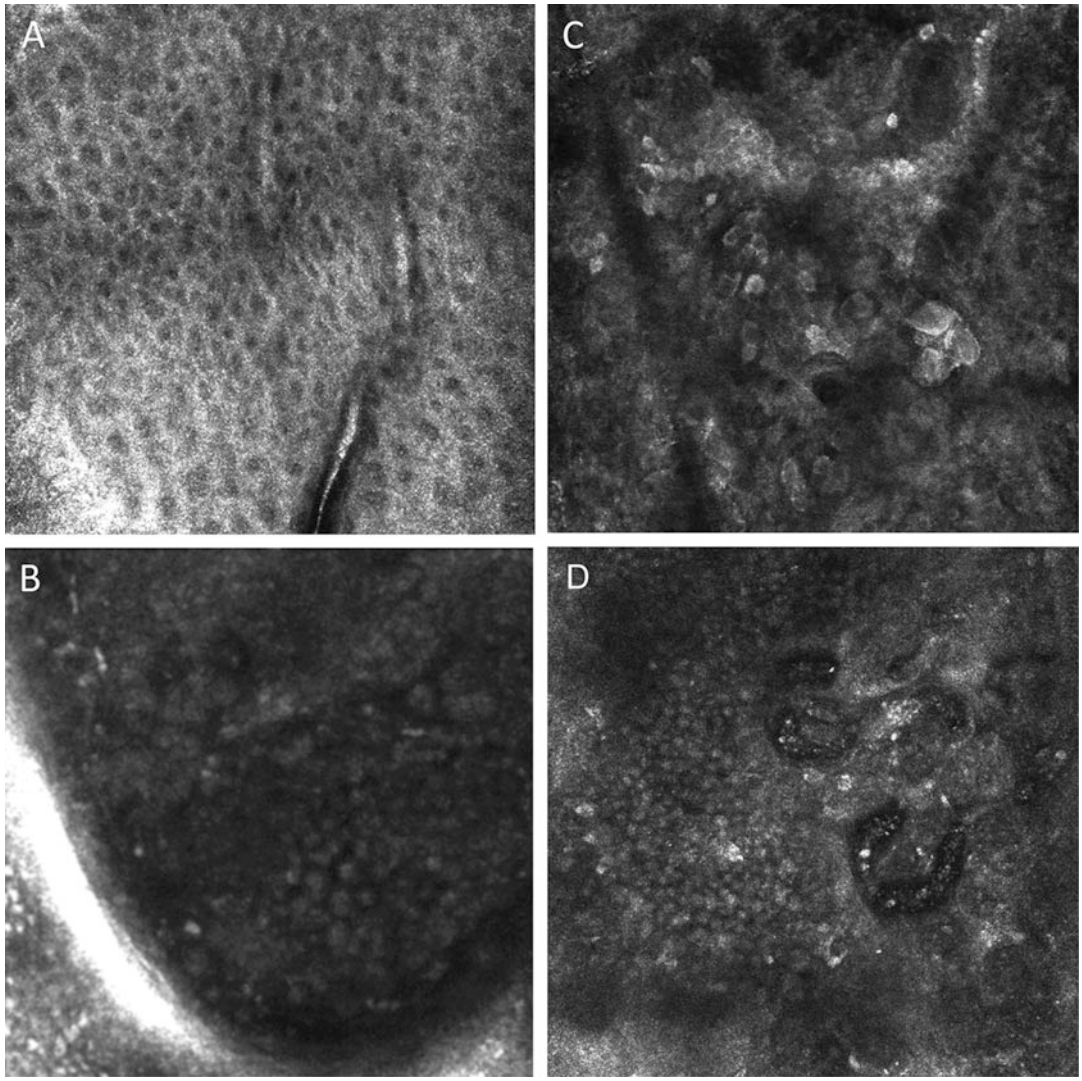

Fig. 33 Confocal characteristics of nodular melanoma. (**a**) Normal epidermis. (**b**) Atypia at the basal layer. (**c**) Cerebriform nests with plump, bright cells. (**d**) Cerebriform nests with vessels

increasing in size to clods, are formed by aggregates of melanin-loaded macrophages. Short lines are then formed by sheets of melanoma cells in the epidermis or upper dermis, and asymmetrical circles of pigmentation around hair follicles, often incomplete circles (crescent-shaped), form as melanoma cells descend unevenly around the hair follicle. As melanoma cells proliferate within the hair follicle and invade the adjacent dermis, streaks join up to form angulated or polygonal lines (zigzag pattern or rhomboid structures). Angulated/polygonal lines increase in thickness until they form structureless zones with hair follicles still evident, followed by structureless zones with hair follicles obliterated (Fig. 35) (Schiffner et al. 2000).

The most widely accepted diagnostic features of LM/LMM were proposed by Stolz et al., who listed primary criteria of dots and circles (annular-granular pattern), slate-gray dots and clods, incomplete pigmented circles around follicular openings, asymmetric changes over time, and the absence of seborrheic keratosis features such as yellow-brown opaque structureless areas, horn

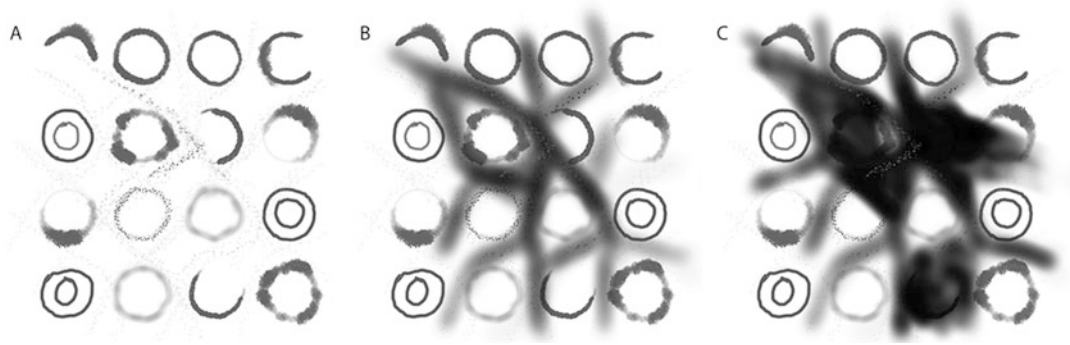

Fig. 34 The Schiffner progression model for lentigo maligna and lentigo maligna melanoma. (**a**) Dots and then clods are formed by aggregates of melanin-loaded macrophages. Short lines and asymmetrical or incomplete circles of pigmentation around hair follicles are then formed by sheets of melanoma cells in the epidermis or upper dermis. (**b**) Lines join up to form angulated or polygonal lines, which increase in thickness until they form structureless zones with hair follicles still evident, (**c**) followed by structureless zones with hair follicles obliterated. (Provided by Ralph P. Braun. CC BY-NC 4.0)

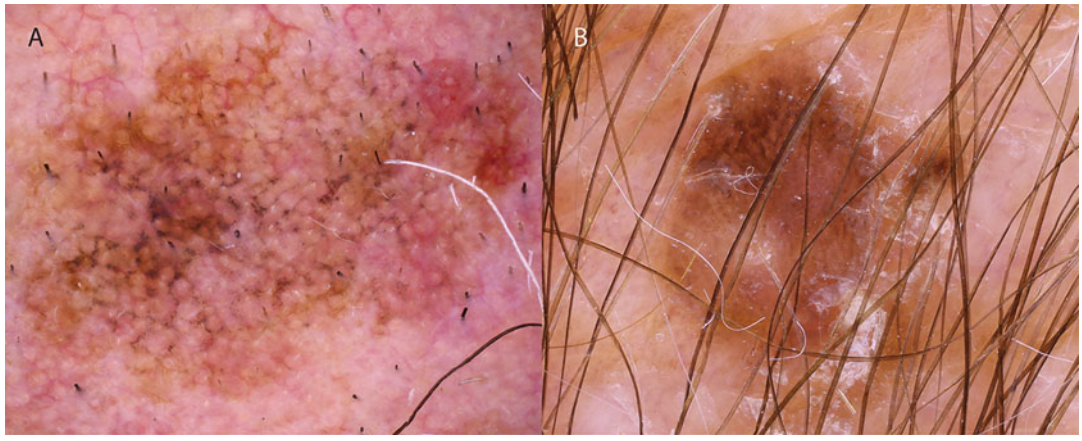

Fig. 35 (**a**) Brown and gray annular-granular structures joining up into incomplete circles around follicles in a lentigo maligna melanoma. (**b**) Angulated lines in a lentigo maligna melanoma

clods (pseudocysts), thin, curved parallel brown lines (fingerprint-like structures), and a sharply demarcated scalloped border (moth-eaten border) (Stolz et al. 2002). However, other researchers have added dermoscopic features to this list that may improve specificity and sensitivity. Schiffner et al. found that a combination of incomplete circles, dark brown or black polygonal lines (rhomboid structures), and slate-gray dots or clods gave a sensitivity of 89% and a specificity of 96% for LM/LMM in a series of 87 patients with pigmented facial lesions (Schiffner et al. 2000). In addition to the Stolz criteria, Pralong et al. found that 125 cases of histopathologically confirmed LM/LMM frequently displayed increased vascular network density (58%), red polygonal lines (rhomboid structures) (40%), and target-like patterns with a dark dot in the center of a hyperpigmented hair follicle (41%) (Pralong et al. 2012). Annessi et al. proposed an algorithm considering irregularly distributed brown clods, a necklace pigment pattern consisting of a fragmented pigment lines with small dots on the lines, reticular lines with irregularly thickened lines, and thick brown or blue-gray lines (ribbon-like structures). In a study of

167 doubtful pigmented lesions on the head, the presence of one or more of these dermoscopic features had a sensitivity of 99% and specificity of 83.9% for LM/LMM (Annessi et al. 2017). Areas of intense pigmentation and darkening on dermoscopy, where the lesion appears darker under dermoscopy than under clinical view, are another sign of LM/LMM. Many of these signs can occur individually in benign facial lesions; however, thick curved lines (cerebriform pattern); an opaque yellow-brown structureless zone; yellow or white clods corresponding to keratin plugs, scales, pseudocysts, white dots, and clods (milia-like cysts); and yellow, brown, or black clods (comedo-like openings) are usually signs of a benign lesion (Table 5) (Annessi et al. 2017; Bollea-Garlatti et al. 2016; Lallas et al. 2016; Peris et al. 2016; Tanaka et al. 2011).

An amelanotic LM/LMM can feature a pink or red homogenous area, pink or red structureless zone interrupted by follicular openings, dotted or irregular linear vessels, whitish structureless areas, or whitish radial lines, with or without traces of pigment. These structures can help distinguish it from clinical mimics such as actinic keratosis or superficial basal cell carcinoma (Giacomel et al. 2014).

Although they occur mostly on the head and neck, 10% of LM/LMM can occur in other heavily sun-damaged areas of the body (Weigert and Stolz 2007). These lesions can mimic superficial spreading melanomas but often retain gray coloring, polygonal lines (rhomboid structures), angulated lines (zigzag lines), incomplete circles, obliteration of follicular openings, concentric circles, blue-gray dots and circles, or increased vasculature (Bollea-Garlatti et al. 2016; Jaimes et al. 2015; Martinez-Leborans et al. 2016; Tiodorovic-Zivkovic et al. 2015).

Reflectance Confocal Microscopy Features of Lentigo Maligna and Lentigo Maligna Melanoma

As with dermoscopy, LM/LMM features on RCM differ from other melanoma subtypes due to the anatomy of the face and the folliculotropism that occurs in LM/LMM. On RCM, the epidermis of LM/LMM is atrophic and characterized by the

Table 5 Features of lesions of the head and neck: lentigo maligna, solar lentigo, and seborrheic keratosis. Several features suggestive of lentigo maligna may also appear in benign lesions

	Dermoscopic appearance
Features suggestive of lentigo maligna	
Gray dots and circles (annular-granular pattern)	Gray dots arranged around a follicle
Slate-gray dots or clods	Irregularly distributed, slate-gray, round to oval, well-circumscribed aggregations of pigment-laden melanophages, over 0.1 mm in diameter
Incomplete circles	Dark brown, thick pigmentation distributed asymmetrically around the follicular openings, often as crescents
Dark brown or black angulated or polygonal lines	Thick brown or black lines between follicles, intersecting to form rhomboid or polygon shapes
Red angulated or polygonal lines	Similarly shaped to brown/black angulated/polygonal lines, formed by increased vasculature between follicular openings
Increased density of vasculature	Thickened red lines of vessels
Central brown dots (target-like or targetoid)	A dark dot in the center of a hyperpigmented hair follicle
Brown clods	Irregularly distributed, brown, round to oval, well-circumscribed pigment aggregations, over 0.1 mm in diameter
Necklace lines	Fragments of thin lines with small dark brown globules on the lines, resembling a necklace
Reticular lines that are thick or that vary in color	Fragments of pigment network with areas of hyperpigmentation and irregularly thickened lines and irregular meshes
Dark brown or blue-gray thick lines (ribbon-like structures)	Dark brown or blue-gray, thick, linear, ribbon-like structures that do not fill the whole interfollicular space; they may intersect to form zigzags or rhomboids
Black structures	Any type of black structure

(*continued*)

Table 5 (continued)

	Dermoscopic appearance
Darkening at dermoscopy	The lesion appears darker under dermoscopic examination than under clinical examination
Features specific to benign solar lentigo or seborrheic keratosis	
Thick, curved lines (cerebriform pattern)	Brain-like pattern of brown, regularly thickened curved lines
Thin, brown, curved parallel lines (fingerprint-like pattern)	A network of fine, light brown lines resembling a fingerprint
Opaque yellow-brown structureless zone	Yellow-brown, homogenous, structureless pigmentation with an opaque surface
Horn pseudocysts or white dots and clods (milia-like cysts)	Irregularly distributed and variously sized white or yellow structures made of intraepithelial horn cysts
Sharply demarcated, scalloped border (moth-eaten border)	Irregular borders with ragged large or small concave indentations, similar to moth-eaten fragment
Sharply demarcated border (jelly sign)	The edge of the lesion is sharply demarcated, resembling the edge of a jelly

presence of large or round pagetoid melanocytes that may or may not disarray the epidermis (Fig. 36a). Dendritic pagetoid cells can also be seen in LM/LMM and can correspond to Langerhans cells, activated melanocytes, or atypical melanocytes. Therefore, the careful assessment of dendritic cells in lesions located on sun-exposed skin is crucial. When these dendritic cells are located at the edges of a fully fledged LM/LMM, especially if they are large, they can correspond to the trailing edge of a LM/LMM (Champin et al. 2014; Yélamos et al. 2017). This is very important when mapping the margins of LM/LMM prior to treatment. Therefore, it is key to evaluate the RCM features from the center to the periphery to put these findings in the right context (Guitera et al. 2013; Yélamos et al. 2017).

In 2010, Guitera et al. described an algorithm to diagnose LM/LMM in which major and minor criteria were taken into account (Table 6). A score of $\geq$2 points has a sensitivity of 85% and specificity of 76% for LM/LMM. However, this score was developed using the wide-probe VS1500 microscope at the center of the lesion. This score has also been validated with the handheld VS3000 microscope (Menge et al. 2016), with the addition of the presence of isolated atypical cells at the periphery of a lesion (Champin et al. 2014; Yélamos et al. 2017).

Since the face tends to have a flattened DEJ with minimal elongation of the rete ridges, in RCM the visualization of edged papillae in normal skin can be more difficult. Hence, in LM/LMM the papillae are poorly defined (Guitera et al. 2010). The presence of large atypical melanocytes, both dendritic and round, surrounding the hair follicles is a key RCM feature for LM/LMM (Fig. 36b) and corresponds to the angulated lines, incomplete circles, and other signs of folliculotropism identified with dermoscopy. Initially, these atypical cells can be dispersed as individual cells, along the outer root sheath epithelium of the hair follicles and the basal layer of the epidermis. As the lesion progresses, the melanocytes become continuous along the basal layer and then develop elongated junctional nests of dendritic cells connected to the hair follicles (Hibler et al. 2017). These structures sometimes adopt the shape of a medusa head when located radially around a hair follicle (Fig. 36c) or adopt a mitochondrial-like appearance when located in parallel (Fig. 36d) (Gamo et al. 2016; Waddell et al. 2018). Another dermoscopic sign of folliculotropism, the circle within the circle, has been recently described to correspond on RCM to pigmented keratinocytes as well as pigmented atypical melanocytes, which results in increased pigmentation of the follicular epithelium as well as increased pigmentation in the rete ridges surrounding the hair follicle (Navarrete-Dechent et al. 2018).

When evaluating the upper dermis of LM/LMM, one can identify increased curled fibers corresponding to solar elastosis (Longo and Pellacani 2016), plump bright cells corresponding to dermal melanophages, as well as atypical nucleated cells within the papillae (Waddell et al. 2018). The latter are generally a sign of dermal invasion (Hibler et al. 2017).

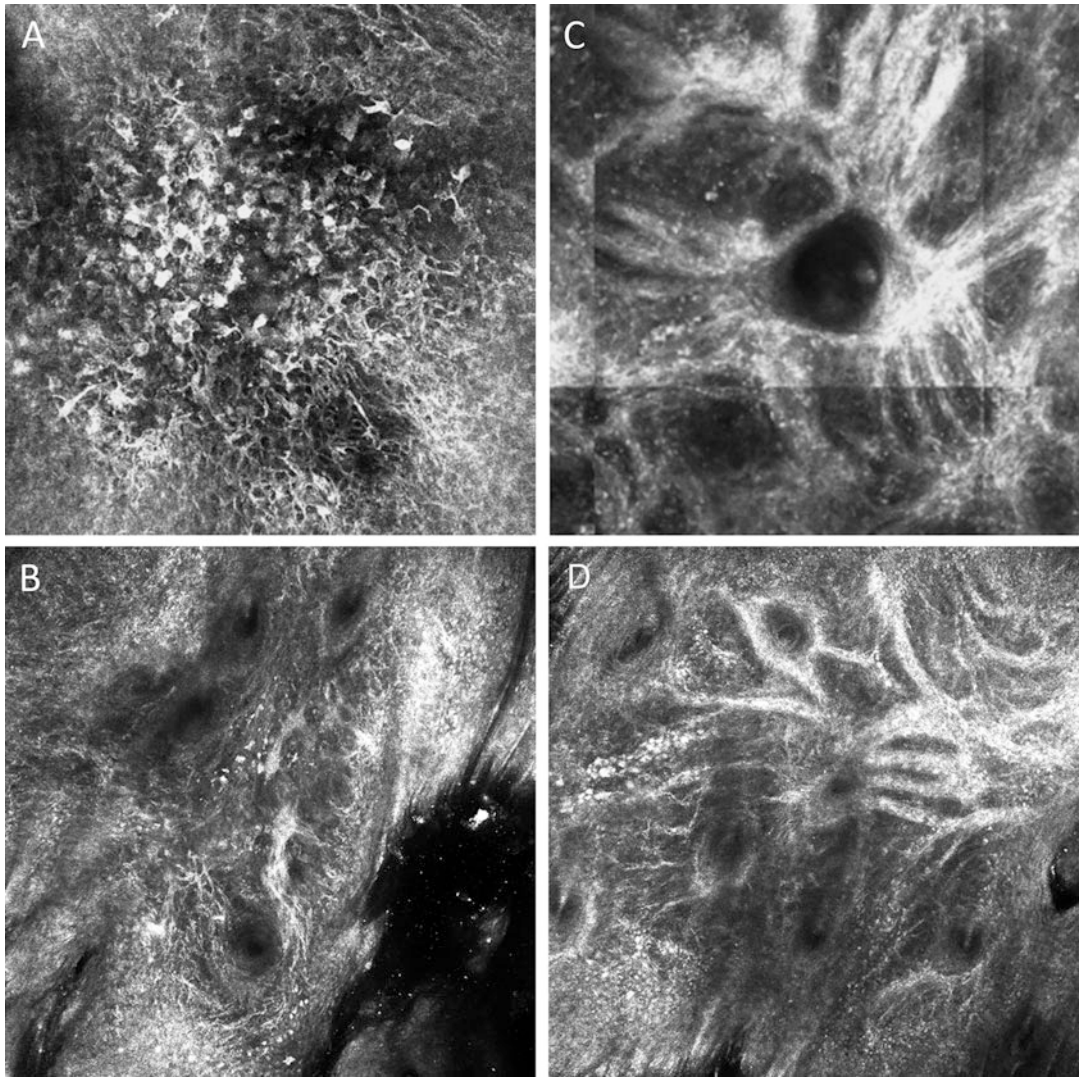

Fig. 36 Confocal characteristics of lentigo maligna and lentigo maligna melanoma. (**a**) Pleomorphic atypical epidermal cells, both round and dendritic. (**b**) Atypical cells at the dermo-epidermal junction, perifollicular dendritic cells, plump cells, and bright cells. (**c**) Medusa head. (**d**) Mitochondria-like structures

Spitzoid Melanomas

Spitzoid lesions exhibit particular unusual dermoscopic characteristics, and exist on a morphobiologic spectrum from frankly benign to benign with atypical features to frankly malignant, possibly reflecting an accumulation of genetic mutations within the lesion. Classical Spitz/Reed nevi present as well-circumscribed, pink-red nodules on the face or extremities of children but can also be found on adults. However, pigmented Spitz/Reed nevi are more common, presenting as well-circumscribed brown-black pigmented macules or plaques that are sometimes verrucous, composed of sharply circumscribed nests of pigmented spindle cells, melanophages, and dendritic melanocytes (Ferrara et al. 2013; Soyer et al. 2001b).

Table 6 Lentigo maligna scoring criteria, with additional features relevant to lentigo maligna and lentigo maligna melanoma

Author	Criteria	Scoring	Interpretation
Guitera et al. (2010)	Major criteria:		Score ≥2 indicates a melanoma
	Non-edged papillae (+2)	2	
	Round large pagetoid cells (+2)	2	
	Minor criteria:		
	Nucleated cells in dermal papillae (+1)	1	
	Atypical cells at the DEJ (+1)	1	
	Follicular localization of atypical cells (+1)	1	
	Broadened honeycomb pattern (−1)	−1	
Champin et al. (2014)	Single large round or large dendritic cell		Should be considered part of the tumor
Yélamos et al. (2017)	Atypical dendritic cell (any size) continuing from the trailing edge		Should be considered part of the tumor

Dermoscopic Features of Spitzoid Melanomas

Three main dermoscopic patterns are characteristic of Spitz/Reed nevi. The majority of Spitz/Reed nevi are pigmented: 51% have a starburst pattern, with a structureless blue-black center and symmetrically distributed radial lines or pseudopods at the periphery. These lines correspond to nests of spindle-shaped melanocytes arranged densely along the dermo-epidermal junction, often with melanophages in the papillary dermis below the nests of melanocytes (Lallas et al. 2017; Soyer et al. 2001b). Seventeen percent have reticular hypopigmented lines around brown clods (negative network); in other nevi, this pattern is considered to be strongly suggestive of melanoma. Here the pigmented clods correspond to pigmented nests of spindle or large epithelioid cells. Other pigmented Spitz/Reed nevi have a globular, homogenous, reticular, or multicomponent pattern (Lallas et al. 2017; Soyer et al. 2001b). Multicomponent pattern consists of irregular or asymmetrically distributed clods, radial lines, or superficial reticular lines and may also have blue structureless zones (blue-white veil); these lesions are very suspicious for melanoma but on histopathological examination may be benign (Ferrara et al. 2013; Soyer et al. 2001b). Nineteen percent of Spitz/Reed nevi are nonpigmented and have a pattern of regularly distributed, monomorphic dotted vessels; a negative network can also exist in these lesions, with the depigmented reticular white lines surrounding a blood vessel. In nodular or raised lesions, the vessels may be seen as larger red clods or coiled, helical (corkscrew), or looped (hairpin) vessels (Lallas et al. 2017).

Management of spitzoid lesions is complicated by the fact the some spitzoid melanomas are indistinguishable dermoscopically from Spitz/Reed nevi (Soyer et al. 2001b). Consensus guidelines by the International Dermoscopy Society (Lallas et al. 2017) state that spitzoid lesions should be managed with both the age of the patient and the dermoscopic features of the lesion in mind. Dermoscopically asymmetric lesions with spitzoid characteristics, whether flat or nodular, are suggestive of melanoma and should be excised, regardless of the patient's age. In addition, any new spitzoid lesion appearing after the age of 12, even when symmetrical, should be excised or closely monitored for dermoscopic changes. For patients under 12 years of age, flat, symmetrical spitzoid lesions should be monitored and excised if there are asymmetric changes; lesions with symmetric changes should be followed up until there has been no new changes or growth for 6 months.

Reflectance Confocal Microscopy Features of Spitzoid Melanomas

Since Spitz/Reed nevus and spitzoid melanomas can present clinically with the same patterns, RCM has been used to help distinguish spitzoid lesions sharing the same dermoscopic patterns. Initially, Pellacani et al. described Spitz/Reed

nevi that presented on RCM with a sharp border, junctional nests, and melanophages (Pellacani et al. 2007b). Later, Guida et al. performed a retrospective study evaluating the RCM features of 34 Spitz/Reed nevi and spitzoid melanomas sharing the same dermoscopic patterns (Guida et al. 2016). They concluded that the features more commonly associated with spitzoid melanoma were (1) the presence of very marked cell pleomorphism in the epidermis, (2) very marked pleomorphism within nests, and (3) atypical cells widespread throughout the DEJ of the entire lesion. However, RCM results when assessing spitzoid lesions should be treated with caution since important histologic features to distinguish Spitz/Reed nevi from melanomas, such as dermal maturation or the present of deep mitoses, cannot be evaluated with RCM.

Desmoplastic Melanomas

Desmoplastic melanoma (DM) is a type of invasive melanoma characterized by a fibrocollagenous stroma with sparsely distributed spindle cells. They are easily mistaken clinically for benign lesions or other skin cancer types, and there is an overlying melanoma in situ component or atypical melanocytic hyperplasia in three quarters of desmoplastic melanomas. DM are commonly located in the head/neck region, and the in situ component is usually lentigo maligna. Clinically, multiple colors are common, particularly pink, red, brown, or white, and DM frequently have either a papular or nodular component or are entirely nodular. Poorly defined borders are another common feature (Jaimes et al. 2013; Maher et al. 2017).

Dermoscopic Features of Desmoplastic Melanomas

Common dermoscopic patterns in DM include typical and atypical reticular and globular patterns and a structureless pattern interrupted by follicular openings (pseudonetwork pattern) on the face. White lines perpendicular to each (crystalline structures) other appear in 80% of DM, and atypical and polymorphous vascular structures are present in over 80% of DM, including dotted, serpentine (linear irregular), or coiled (glomerular) vessels and pink structureless zones. Other common dermoscopic features of DM are gray dots (peppering), gray dots with gray circles (annular-granular pattern), incomplete circles (asymmetrically pigmented follicular openings), blue structureless zones (blue-white veil), irregularly distributed clods, reticular lines that vary in thickness or color (atypical network), white structureless zones (scar-like areas), off-center dark structureless zones, and peripheral light brown structureless zones. Negative network, radial lines (streaks), polygonal lines, and structureless zones with obliterated follicles are occasionally seen in DM (Jaimes et al. 2013; Maher et al. 2017).

Reflectance Confocal Microscopy Features of Desmoplastic Melanomas

Confocal features that are common in superficial spreading melanomas are also found in DM. Pagetoid cells, cellular atypia, and nucleated cells in the dermis are all found in the majority of DM. A study of 37 DM found that the Modena algorithm (Pellacani et al. 2007b) had a 97% sensitivity for DM. However, several confocal features are DM-specific. Spindle cells in the superficial dermis, inflammation in the dermis, and vertical vessels in the papillae are more common in DM. Round pagetoid cells are less common in DM than in other invasive melanomas (Maher et al. 2017).

Conclusion

The development of noninvasive diagnostic tools such as dermoscopy and RCM, and the corresponding improvement in diagnostic accuracy, has marked an important step forward in melanoma diagnosis. Dermoscopy in particular has been shown to be useful to primary care physicians and dermatologists after a short training course, while RCM allows very detailed examination of equivocal lesions in sensitive areas and mapping the edges of lesions prior to excision, reducing the number of excisions required.

Ongoing research with these tools has revealed in detail the most common dermoscopic and confocal features of melanoma while also determining the features of difficult-to-diagnose lesions such as nodular melanoma, spitzoid melanomas, or lesions on unusual body sites such as facial or acral skin.

Cross-References

- Acral Lentiginous Melanoma
- Classification and Histopathology of Melanoma
- Clinical Presentations of Melanoma
- Melanoma Prevention and Screening
- Mucosal Melanoma

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