Chapter IV.3

Amelanotic Melanoma

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IV.3

Contents

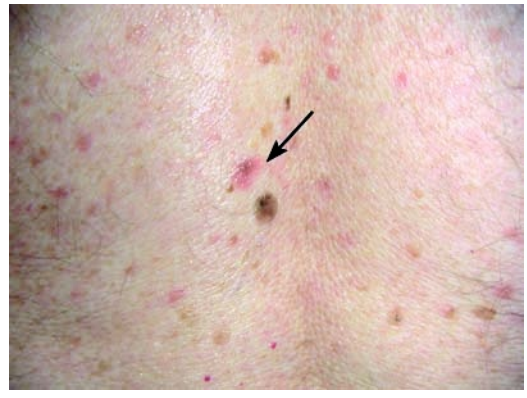


Fig. IV.3.1. Amelanotic melanoma (*center*; SSM, L III, 0.6 mm)

IV.3.1 Introduction and Definition

"Amelanotic melanoma" is a clinical and descriptive term frequently used for any melanoma lacking melanin pigmentation. These tumors represent a large fraction of the so-called "featureless" or "undiagnosable" melanoma [3–5, 7, 13]. This chapter gives details on the dermoscopic features of amelanotic melanoma which may help to classify the variety of tumors summarized under this general term; however, amelanotic melanoma will not be identified by dermoscopy nor by any other diagnostic method if a lesion is not considered worth inspection with the particular instrument – a screening strategy including knowledge of clinical features, dermoscopic techniques and criteria is essential to spot amelanotic melanoma among the variety of non-pigmented lesions of the skin (Figs. IV.3.1, IV.3.5a).

IV.3.2 Hypomelanotic and Amelanotic Melanoma

Frequently, melanoma are classified "amelanotic" regardless of the degree and nature of hypopigmentation. One must distinguish two reasons for a melanoma to contain little melanin. There are tumors which produce little or no melanin. On the other hand, there are melanoma which have lost more or less of their melanin

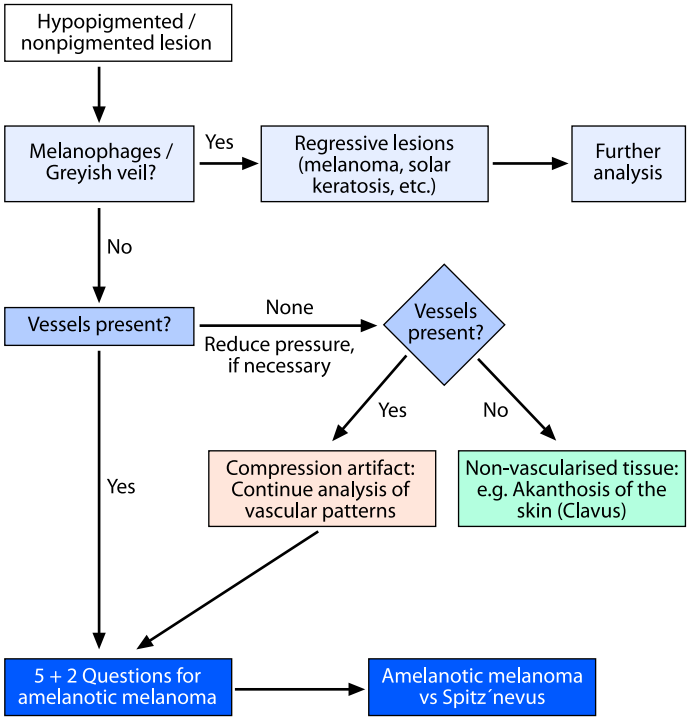
content mostly due to regression. Both phenomena may even occur within the same lesion. The varied reasons for hypopigmentation should find their equivalent in clinical and, more importantly, in dermoscopic terminology.

IV.3.4 Clinical Features

Completely amelanotic melanoma are quite rare: estimates between 2 and 8% are given [14]. In general, the descriptive clinical term "amelanotic" melanoma is used imprecisely, as it is frequently attributed to a wide variety of tumors with a broad spectrum of intensity and variable distribution of their pigmentation. Hypopigmentation may refer to the entire lesion or just to a segment of the tumor, and may develop or change with time [8]. One should differentiate between tumors lacking melanin just in circumscribed segments, and other ones which are of homogenous structure and contain little melanin within the entire lesion. The extreme variant of the latter are completely "amelanotic" melanoma. A lesion containing a low amount of melanin in all segments warrants description as "slightly pigmented melanoma." Lesions with circumscribed hypopigmentation may be characterized as "partially hypomelanotic" or "partially amelanotic" melanoma (Table IV.3.1).

There exist tumors with great differences in melanin content, be it the proportion of the hypopigmented area in partially pigmented melanoma or the intensity of pigmentation within a slightly pigmented melanoma. As a proposal, a melanoma may be considered "partially pigmented" if the section containing melanin is no larger than 30% of the tumoral area. A melanoma should be described as "slightly pigmented" if the intensity of pigmentation is an estimated 30% of a "regular" dark-brown tumor as judged by visual inspection. Colorimetric and quantitative measurements of these details appear desirable for classification of melanoma for scientific purposes.

Regressive melanoma may best be spotted by means of grayish or whitish areas, the white areas being whiter than the neighboring skin. Reports of the patient that a dark spot or nodule has become paler may be helpful.



Flow-chart IV.3. For classifying hypopigmented melanoma and diagnosing amelanotic melanoma

Table IV.3.1. Phenotypes of hypomelanotic and amelanotic melanoma

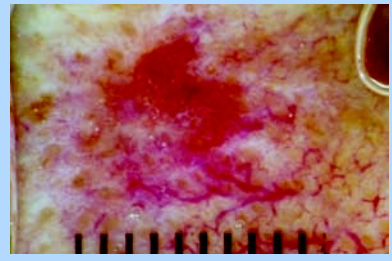
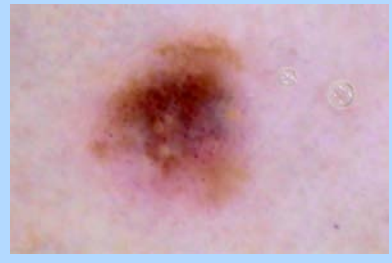
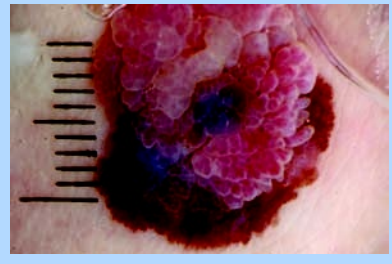
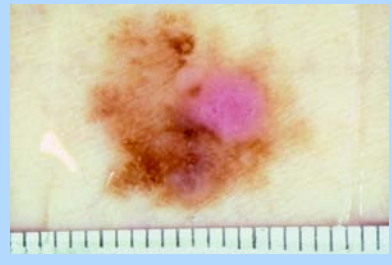
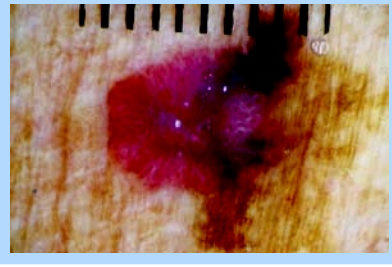
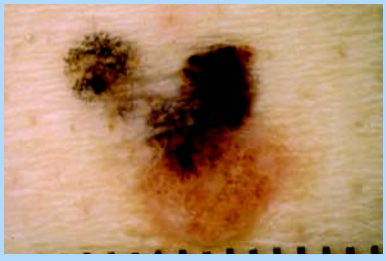
Description of lesion	Category of melanoma	
Melanoma not producing any trace of melanin	Amelanotic melanoma (*sensu strictu*)	
Melanoma consisting exclusively of a cell line with low production of melanin	Hypopigmented melanoma	
Melanoma consisting of a section (mostly a nodule) with no or little melanin content within a pigmented tumor	Partially pigmented melanoma	
Hypomelanotic melanoma with amelanotic components	Partially pigmented melanoma	
Amelanotic / hypomelanotic melanoma associated to junctional or compound nevus	Partially pigmented melanoma	

Table IV.3.1. (*continued*)

Description of lesion	Category of melanoma	
Partially regressive melanoma associated to dermal nevus	Partially pigmented melanoma	
Amelanotic cell line/metastasis in regressive melanoma		No images available
Collision tumors of amelanotic melanoma and non-pigmented lesions (e.g. BCC, seborrheic keratosis)		No images available

In order to complete the listing of hypopigmented variants of melanoma, collision tumors of a regressive or amelanotic melanoma (or a melanoma metastasis) next to or within a poorly pigmented benign lesion, e.g., a dermal nevus or a seborrheic keratosis, might be taken for an amelanotic melanoma despite the fact that the components are of different origin and biological behavior. Such cases of collision tumors are somewhat hypothetical and certainly very rare. They are not dealt with any further here.

IV.3.5 Dermoscopic Criteria

There are few reports in the literature which describe dermoscopic features of truly amelanotic melanoma [1, 2, 6, 12, 14, 15]. The diagnostic importance of vascular structures is stressed in each contribution. In several papers cases of hypomelanotic melanoma due to regression are viewed jointly with completely amelanotic melanoma; however, intermingling melanoma with different origin of hypopigmentation in morphological studies will result in loss of sensitivity and specificity of features. It is therefore suggested to follow the pathway given in this chapter to distinguish the two basic types of hypomelanotic melanoma before analyzing the morphology any further.

Loss of melanin due to regression can be recognized easily in almost any case, as it is indicated by the presence of melanophages visible as tiny grayish granules of approximately 0.01–0.02 mm diameter ("peppering"), or by the presence of gray-blue veils. Progress of regression results in disappearance of grayish areas and melanophages, leaving behind whitish fibrous tissue resembling a scar. These lesions should be excluded from the suspicion of amelanotic melanoma. They show differences in vascularization as compared with amelanotic melanoma.

Truly amelanotic melanoma do not contain any melanin; thus, all features related to details of pigmented lesions must be absent. Size, asymmetry, irregular border, and ulceration are features of secondary diagnostic importance as they are not restricted to melanocytic tumors; however, as vascular structures are easily visible, amelanotic melanoma can be diagnosed with a dermoscope, provided they are inspected properly.

Theoretically, there might exist melanoma consisting of a regressive section joint with an amelanotic component (and even in collision with further hypopigmented tumors such as seborrheic keratoses or basal cell carcinoma). They must be identified by stepwise analysis of the various components and certainly are a challenge even for the experienced dermoscopist.

IV.3.6 Adequate Dermoscopic Inspection of Non-pigmented Lesions

Instruments with glass front plate must be set onto the tumoral surface very carefully in order to avoid compression of the soft vascular structures and squeezing out the blood, rendering them invisible. Ultrasound gel is recommended as a contact medium due to its low viscosity and non-volatility. This helps to inspect the vessels with as little pressure as possible. Use of instruments with polarized light may serve better if the light source emits an appropriate spectrum of wavelengths for visualizing reddish structures such as blood vessels and the magnification permits viewing small capillaries of 10 µm in diameter; however, most dermoscopes using polarized light operate with low magnification, which is inadequate for analysis of vascularization. If a non-pigmented lesion does not reveal any vessels upon dermoscopic inspection, the first idea should be to control the pressure of the instrument. Any non-pigmented lesion (with the exception of, for example, hyperkeratoses) must present at least some vascular structures upon appropriate examination. In the literature one finds many cases with obvious compression artifacts: no vessels are visible within whitish areas, preferably within the most elevated regions of nodular lesions.

IV.3.7 Dermoscopic Features of Amelanotic Melanoma

In truly amelanotic melanoma all features related to pigmentation are absent. Observations of grayish veils, traces of network, etc., refer to regressive, hypomelanotic or partially hypo-/amelanotic melanoma. If reddish or pink areas are observed, the magnification might be too low to distinguish terminal capillaries, or the vessels might be out of focus; therefore, instruments permitting focus control are quite helpful for better analysis of vascular structures. The only features visible dermoscopically are vessels and whitish structures which resemble pseudohorn cysts (Fig. IV.3.5b); the latter are somewhat misleading, as they might be taken as signs of seborrheic keratoses, basal cell carcinoma, or ordinary nevi. They are present in melanoma of several millimeters in vertical diameter. In histological sections they revealed mucoid degeneration and no keratin (unpublished observations); thus, the remaining features of diagnostic importance are vascular patterns.

IV.3.8 Vascular Patterns in Amelanotic Melanoma

The vascular patterns in amelanotic melanoma have been described as pinpoint, point-like, dotted vessels, and as hairpin, loop-like, linear irregular vessels. In principle, all point-like or looped vessels are variants of the basic structure of a vascular loop; however, loop-like terminal capillaries are encountered in melanocytic lesions (Spitz nevi, melanoma) [5] as well as in all keratinizing lesions (vulgar warts, seborrheic keratoses, keratoacanthoma, squamous cell carcinoma, etc.). Of course, vessels encountered in dermal papillae are not to be considered as tumoral vessels. The appearance of vascular loops depends on their length and the angle of viewing them. Upon viewing in axial direction, vertical to the tumoral surface, short loops are visible as tiny red dots. Longer loops resemble hairpins, especially if the direction of view is somewhat oblique. Increasing tumoral thickness requires elongation of the feeding vessels. The longer the vascular loops, the more morphological variations are to be seen. Twisting, splintering, glomerular-like winding of the loops is observed; however, a loop is the basic structure of these peculiarities. There is a tendency to describe too many details within the vascular structures, thus confounding the observers. Another descriptor of vessels is the

mode of their arrangement within the tumor, e. g., regular or irregular, arranged at the periphery or distributed evenly over the tumoral surface, etc. Vascular loops (point-like rather than hairpin-like) in amelanotic melanoma are dispersed quite regularly across the entire area of the tumor; however, this is the case only in early lesions.

IV.3.9 Morphological Changes of Vessels During Tumor Growth

The fact that dermoscopic analysis of vessels in melanoma must consider time-dependent changes which occur during tumor growth has attracted too little attention: As horizontal diameter and vertical thickness of melanoma increase with time, vessels in advanced stages will be longer, coarser, and more variable according to the tumoral thickness. Examples for the evolution of vascularization of melanoma are given in Figs. IV.3.2–IV.3.5. All thin melanoma (<0.5 mm Breslow thickness) are supplied by point-like vessels in a quite regular arrangement across the entire tumoral area (Figs. IV.3.2, IV.3.3). Tumors of 0.5- to 2-mm thickness reveal vessels of point-like and hairpin appearance, yet the arrangement of vessels is quite regular (Fig. IV.3.4). Beyond 2 mm thickness, the hairpin loops become increasingly more twisted and splintered, and their arrangement is not as regular as in thin tumors; hence, they were described as irregular vessels (Figs. IV.3.3, IV.3.5a,b). Melanoma of more than approximately 3 mm thickness develop a different structure of vascular supply. As vertical growth apparently cannot be maintained by further elongation of the capillary loops, vessels arising from the adjacent dermal plexus appear on the tumoral surface. These vessels resemble arborizing vessels of basal cell carcinoma; however, their winding and branching is less bizarre and irregular as compared with basal cell carcinoma. Reports published on amelanotic melanoma frequently note that tumors were ulcerated [7, 10, 13]. This secondary phenomenon may disturb the morphology of the vessels and make it more difficult to characterize them. Studies frequently report a surprisingly low percentage of amelanotic melanoma with visible vascularization. This may be ascribed to non-standardized imaging techniques and low magnification, and to mixing truly amelanotic, regressive, and hy-

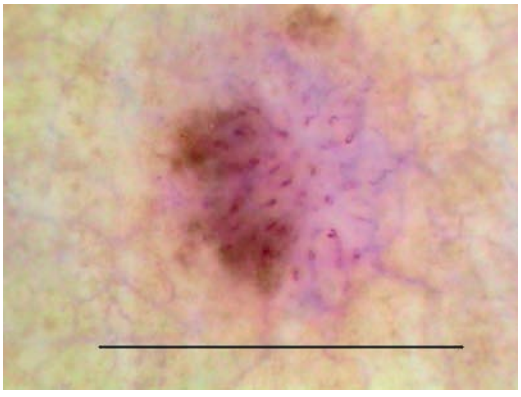


Fig. IV.3.2. Partially pigmented, hypomelanotic melanoma (SSM in situ). *Bar:* 5 mm

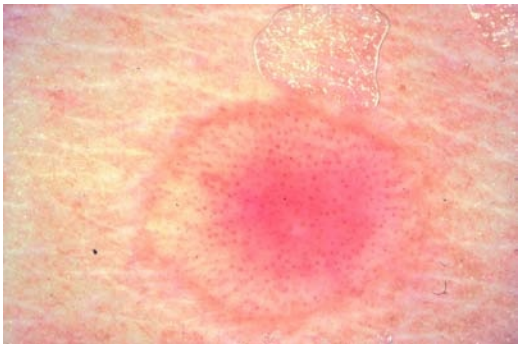


Fig. IV.3.3. Amelanotic melanoma (SSM, L III, 0.4 mm)

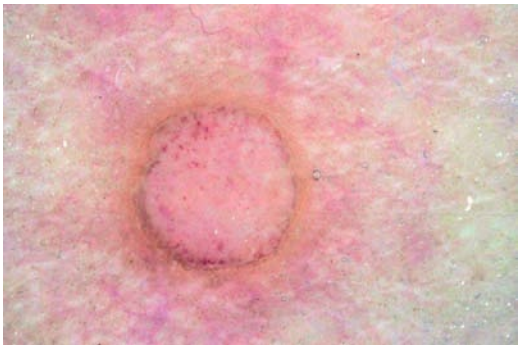


Fig. IV.3.4. Amelanotic melanoma (NM, L IV 1.2 mm)

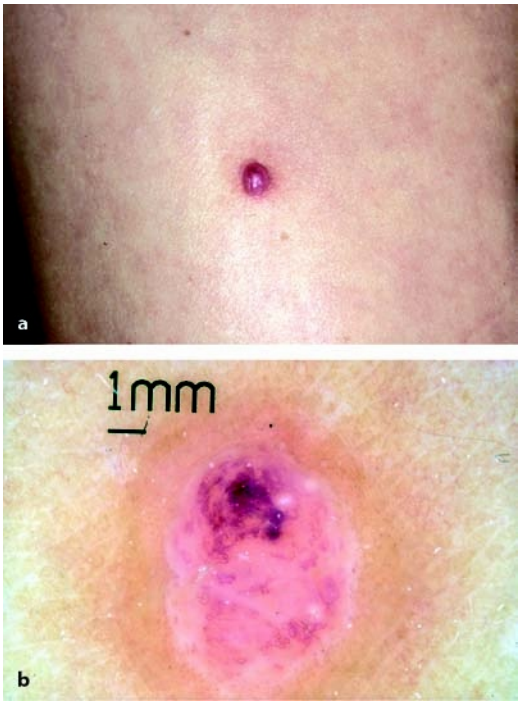


Fig. IV.3.5. **a** Amelanotic melanoma (NM, L IV, 2.8 mm). **b** Amelanotic melanoma (NM, L IV, 2.8 mm): irregular vessels, some of hairpin shape. Note absence of white halo and presence of whitish spots. Histopathology: no pseudo-horn cysts but mucoid degeneration

pomelanotic melanoma. Nevertheless, the importance of vascular structures is underlined. Pizzichetta et al. [14] consider vascular patterns the only relevant ones for diagnostic purposes. The presence of point-like, hairpin-like, linear, and linear-irregular vessels is reported. Diameter, asymmetry, and ulceration are considered less valuable for diagnosis.

Few studies separate thin (<1 mm) and thick (>1 mm) melanoma [2, 14]. One of the few papers which deals with amelanotic melanoma of low thickness is that by Bono et al. [2], with the prevailing vascular pattern in accordance with own observations being dotted vessels. This pattern appears to be the most valuable for identification of early amelanotic melanoma. Other studies present cases of considerable thickness, mostly more than 1 mm [15]. As explained above, vessels in these lesions tend to be split, splintered, and twisted, thus appearing "atypical" and "irregular." As a rule – and surprisingly – advanced cases of amelanotic melanoma may be more difficult to identify by dermoscopy than early lesions of low vertical diameter.

IV.3.10 Relevant Clinical Differential Diagnosis

Confounding amelanotic melanoma and basal cell carcinoma should not occur if the vascular patterns are viewed correctly – arborizing vessels of basal cell carcinoma can easily be distinguished from point-like or loop-like vessels. The vascularization of dermal nevi consists of coarse and "comma-shaped" vessels in a surprisingly irregular arrangement. The vessels in pyogenic granuloma appear blurred and are of unspecific morphology. In regressive tumors (regressive melanoma as well as in regressive solar keratoses, "lichenoid" keratoses, etc.) the vascular pattern also cannot be ascribed to a certain geometrical structure.

Keratinizing tumors represent a large group of non-pigmented lesions and their loop-like vessels may resemble the ones of amelanotic melanoma. Depending on their vertical diameter, flat lesions display point-like vessels, whereas thicker ones are supplied by hairpin-like longer loops. Characteristically, in all keratinizing tumors the vessels are embedded into a whitish halo. The halo represents the vital keratinocytes supplied by the feeding capillary. The whitish zone in most cases merges into a yellowish substance, which is keratin. This observation is most helpful for excluding non-pigmented lesions from suspicion of melanoma. An instrument more powerful than just tenfold magnification is particularly helpful for viewing faint white halos.

IV.3.10.1 The Way to Diagnosis of Amelanotic Melanoma

A pathway to diagnosis of amelanotic melanoma based exclusively on analysis of vascular structures was published in 1996 [9, 11]. It is applicable to truly amelanotic melanoma provided the lesions are not ulcerated. Regressive mela-

noma and compression artifacts should be excluded by means of the procedure summarized in the flow chart below.

Analysis of vascularized lesions can be summarized in a series of 5 + 2 questions leading directly to diagnosis. This pathway is best applicable to flat lesions. In cases of thick, pink, and nodular tumors one must always consider the morphological changes in vascular patterns, rule out frequently occurring non-pigmented lesions as mentioned above, and treat the remaining ones with special attention.

In the list below the presence of a certain type of vessel is asked for – if the answer is "no," one may proceed to the next question:

1. Presence of arborizing vessels (basal cell carcinoma)?
2. Presence of crown vessels (sebaceous hyperplasia)?
3. Presence of "comma" vessels (dermal nevus)?
4. Presence of unspecific vessels (Kaposi sarcoma, regressive lesions)?
5. Presence of point-like or hairpin vessels?

5.1 Absence of white halos?

5.2 Presence of traces of melanin?

If question no. 5 is answered, in the affirmative (i.e., presence of point-like or loop-like vessels), additional questions must ask for the absence of white halos and presence of traces of melanin. If the answer is "yes," suspicion of melanoma is raised. If traces of brownish melanin, which may not be visible clinically, are present focally within the lesion, they support the diagnosis of melanoma or Spitz nevus, the only other diagnosis, which has to be considered. It is very difficult, often impossible, to discriminate reliably amelanotic melanoma and Spitz nevus by dermoscopy. As histopathological judgment faces the same problem, consequently all lesions with point-like or loop-like vessels without white halo must be considered suspicious and removed.

IV.3.10.2 Strategies for Detecting Amelanotic Melanoma

Spotting amelanotic melanoma is one of the challenges for a dermatologist and possibly a life-saving diagnostic procedure if performed early enough. It is not possible to identify these tumors positively by clinical criteria; however, in the present author's opinion, dermoscopy is effective in diagnosing suspicious lesions in almost all cases of amelanotic melanoma, especially early ones. But dermoscopy is not the first step in diagnosing amelanotic melanoma. The major obstacle in our own strategy in selecting lesions for dermoscopic examination is that we have been trained to consider large and dark tumors as suspicious, and the idea of using a dermoscope arises when we come over such lesions. Small and non-pigmented objects escape our attention and are not considered worthy of further examination. This approach represents a filter mechanism toward large and dark lesions. Small and hypopigmented lesions ("atypical melanoma") are neglected. "Atypical melanoma" frequently are not examined by dermoscopy and neither photographed nor excised, thus escaping early diagnosis and our visual memory. Most studies are based on cases of melanoma with high thickness, mostly reddish or pink nodules, frequently ulcerated [10, 13], which are eye-catching. The lack of images of early non-pigmented melanoma leads us back to diagnostic recommendations and procedures, and reddish macules too frequently are not inspected dermoscopically. In the working routine of the present author, elimination of the amelanotic melanoma filter mechanism, i.e., not restricting dermoscopy to large and dark tumors ("pigmented lesions of the skin"), has changed the spectrum of melanoma phenotypes. This approach, best described as "non-selective dermoscopy," has raised the proportion of poorly pigmented melanoma to a constant of 20% of all cases per annum during the past 7 years, among them 6% truly amelanotic melanoma (unpublished observations).

Core Messages

- Do not restrict dermoscopy to large and pigmented lesions.
- Regressive melanoma present different features as compared with amelanotic melanoma. Rule them out by using flow chart 1.
- When viewing a non-pigmented lesion make sure the instrument does not exert pressure onto the vessels.
- Lesions with visible vascularization should be analyzed with the (5 + 2) questions procedure.
- Lesions with point-like or loop-like vessels lacking a white halo must be considered suspicious for amelanotic melanoma or Spitz nevus.
- Remember that nodular lesions are particularly difficult to analyze: vessels of pyogenic granuloma are blurred and barely visible, and lesions with vessels characteristic for basal cell carcinoma, dermal nevus, and keratinizing tumors help to rule out these diagnoses. The remaining lesions have to be dealt with carefully, as melanoma cannot be ruled out.
- There are no "featureless" melanoma: a lesion "without features" must be re-examined, as you have probably missed them.

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