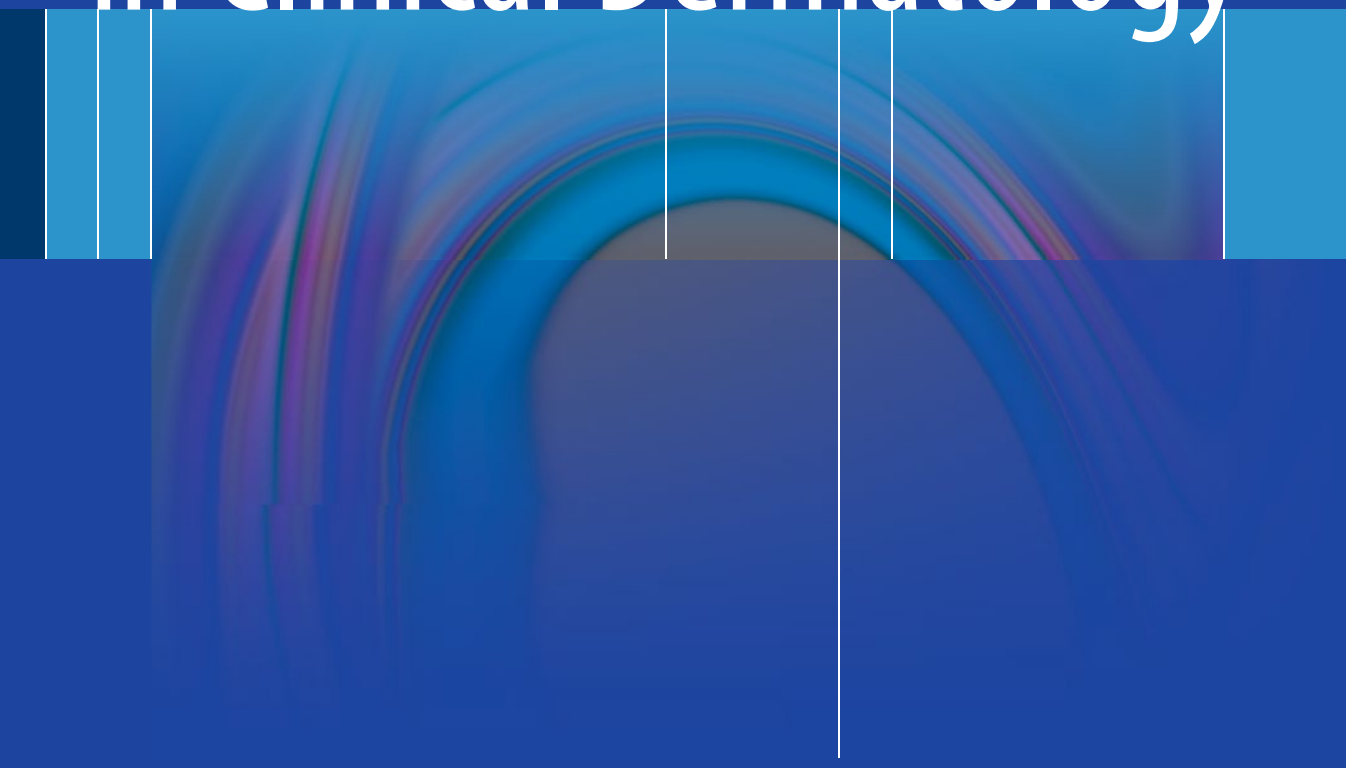
Enzo Berardesca
Howard Maibach
Klaus-Peter Wilhelm
Editors

Non Invasive Diagnostic Techniques in Clinical Dermatology



Springer

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Preface

This project has been undertaken to update the book on Methods and Instrumentation released in the series on "Bioengineering and the Skin" in 1995. However, during the revision process we realized that so much time has passed and many new techniques were developed that it was almost impossible to update the old edition; therefore, on the basis of the previous experience, we devised a table of contents covering not only the "old" and "classic" noninvasive techniques, but focusing on also both new methods and techniques developed recently. The reader will find a new broad section on skin imaging based mainly on techniques developed in recent years, a wide approach to methods for investigating the stratum corneum and the superficial layers of the skin, as well as sections dedicated to particular skin sites of specific interest such as hair and nails. Indeed, the field in this decade has expanded not only from a technical viewpoint in new hardware but also in new applications of existing technology developed to investigate specific areas of "transferred" technology (i.e., from biochemistry or molecular biology) to noninvasively detect and quantify molecules in superficial skin layers to monitor skin reactions. This book remains a small, intuitive, and easy-to-read tool for dermatologists, biologists, pharmacologists, and scientists in general who are willing to approach skin research and noninvasive skin investigation in particular.

Rome, Italy — E. Berardesca
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Part I

Imaging Techniques

Use of Videodermatoscopy in Dermatology

1

Francesco Lacarrubba, Franco Dinotta, Cecilia Santagati, and Giuseppe Micali

1.1 Introduction

Videodermatoscopy (VD) is a noninvasive technique that allows a rapid and magnified in vivo observation of the skin surface with the visualization of morphologic structures invisible to the naked eye [1–3]. Images obtained by a high-resolution color video camera, equipped with lenses that currently allow magnifications ranging from ×10 to ×1,000, are indirectly visualized on a monitor and stored on a personal computer. This technique allows eventual image processing and comparison of any lesion changes over time, thus significantly improving follow-up assessment. VD represents the evolution of dermatoscopy (also known as dermoscopy), performed with manual devices, which does not require any computer "assistance" but generally reaches magnifications no greater than ×10. VD may be performed directly or, most often, through the technique called epiluminescence microscopy, which involves the application of a liquid transparent medium (oil, gel, alcohol, or water) between the lens and the skin to minimize surface light reflection from the cornified layer. Some systems utilize polarized light, obtaining similar results without the need for liquids. In addition, VD system may be equipped with filtered wavelengths. For instance, a 400 nm light source may be used to obtain imaging enhancement, improving vessel details visualization, for the evaluation of skin microcirculation [4].

VD is widely used in the diagnosis of pigmented skin lesions, as well as in a wide variety of dermatologic conditions (Table 1.1). It may also be useful for prognostic evaluation and monitoring of response to treatment, representing an important and relatively simple aid in daily clinical practice.

In this chapter we will use the term VD, even for those cases in which studies have been performed using manual low-magnification devices.

1.2 Pigmented Skin Lesions

VD allows the identification of different skin structures localized from the epidermis to the superficial/medium dermis usually undetectable by simple clinical observation. Several studies correlated the VD features (retrieved by horizontal observation) and the correspondent histopathologic findings (observed in vertical extension). The introduction of VD has forwarded a great impact in the management of pigmented skin lesions, significantly improving the early detection of melanoma and increasing diagnostic accuracy from 5 to 40 % over clinical visual inspection, depending on lesion type and physician experience [5–9].

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The classic approach to a pigmented lesion by VD is based on a two-step procedure (Fig. 1.1).

The observer should first distinguish melanocytic lesions from non-melanocytic ones. In Tables 1.2 and 1.3, the common VD features of melanocytic and non-melanocytic lesions are described, along with their histopathologic correlation (Tables 1.2 and 1.3). The presence of pigmented network, aggregated globules, streaks, and homogeneous blue pigmentation favors a melanocytic lesion (excluding face, palms, and soles). Moreover, if the lesion does not demonstrate any of the specific structures of non-melanocytic lesion, it should be considered melanocytic and consequently excised to rule out a structureless melanoma [10–13].

The evaluation of vascular structures (Table 1.4) is also useful, especially for the diagnosis of hypo- or nonpigmented lesions [14].

Once a lesion is classified as melanocytic, the second step differentiates benign melanocytic lesions from malignant ones (Table 1.5): in this case, several diagnostic methods may be used. Pattern analysis, first proposed in 1987 and later modified [10, 15, 16], is based on subjective, qualitative, critical, and simultaneous evaluation of several criteria: general appearance of the pigmented skin lesion (uniform or heterogeneous), pattern of pigmentation (type and distribution of color, presence of depigmentation, pigment network, brown globules, and black dots), and lesion margins (regular or irregular for the presence of streaks). Pattern analysis evaluation requires special knowledge of the criteria and specifically trained observers in order to be used with confidence. To make the approach more functional, new diagnostic algorithms have been introduced. They consist of score systems that can be used by less experienced observers, providing a high rate of diagnostic accuracy [6, 11, 17, 18]. They include the ABCD rule, the Menzies method, the seven-point checklist, the CASH (color, architecture, symmetry, and homogeneity) method, and the three-point checklist [19–21]. Pattern analysis, although complex, is the most rapid and complete approach. When the observer achieves good dermoscopic experience, this application becomes intuitive and automatic; it is of great utility, especially in patients with multiple lesions [5].

Table 1.1 VD applications in dermatology

Pigmented skin lesions
Melanocytic (nevi, melanoma)
Non-melanocytic (solar lentigo, seborrheic keratosis, dermatofibroma, basal cell carcinoma)
Nonpigmented skin lesions
Sebaceous hyperplasia
Pyogenic granuloma
Clear cell acanthoma
Xanthomatous neoplasms
Mastocytosis
Sarcoidosis
Median raphe cysts
Eccrine poroma
Keratoacanthoma
Actinic porokeratosis
Nonpigmented facial actinic keratosis
Bowen's disease
Invasive squamous cell carcinoma
Kaposi's sarcoma
Ectoparasitoses
Scabies
Head and pubic lice
Tungiasis
Cutaneous leishmaniasis
Furuncular myiasis
Demodicosis
Cutaneous/mucosal infections
Molluscum contagiosum
Cutaneous warts
Genital warts
Tinea nigra
Lupus vulgaris
Inflammatory disorders
Psoriasis
Lichen planus
Urticaria and urticarial vasculitis
Rosacea
Pityriasis lichenoides et varioliformis acuta
Scalp disorders (see Chap. 39)
Hair loss
Parasitoses
Psoriasis
Hair shaft disorders
Nail disorders
Psoriasis
Onychomycosis
Onychomatricoma
Glomus tumor
Vascular disorders
Port-wine stains
Infantile hemangioma
Pigmented purpuric dermatoses (PPD)

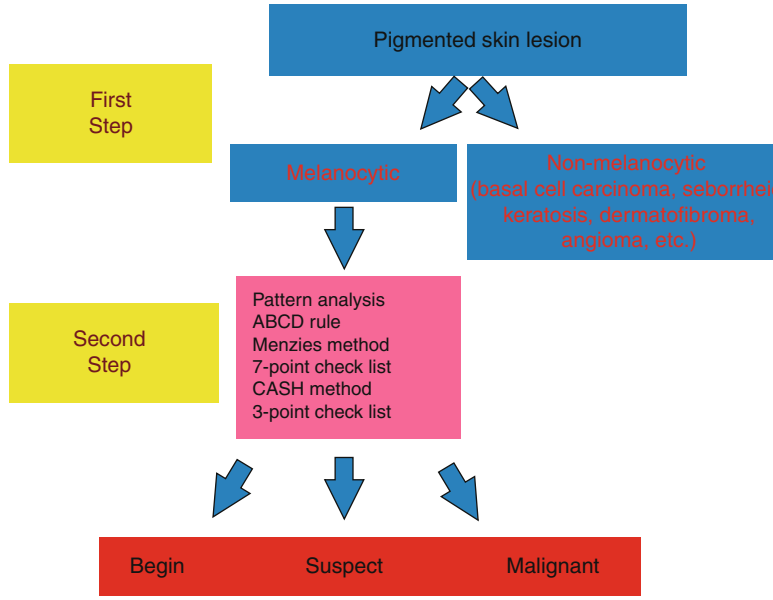


Fig. 1.1 Two-step approach for the diagnosis of pigmented skin lesions

If a non-melanocytic lesion is recognized in the first step, no further evaluation through algorithm methods is needed, as the diagnosis is generally readily made (Table 1.6).

In general, VD examination may confirm or exclude the clinical diagnosis, significantly downsizing unnecessary removal of benign, but clinically equivocal, pigmented skin lesions, such as thrombosed angiomas and seborrheic keratoses. On the other hand, VD may help to increase the index of suspicion in case of melanomas clinically mimicking benign lesions [5].

VD allows close, noninvasive follow-up of pigmented skin lesions in order to detect minimal changes suggesting an early diagnosis of melanoma; monitoring may reduce the number of unnecessary biopsies, representing a helpful tool to decide which lesions should be removed and when. Long-term follow-up allows comparison of atypical nevi over 6–12 months in patients with multiple lesions (i.e., patients with atypical mole syndrome). Short-term follow-up (generally at 3 months) is performed on single suspicious lesions (i.e., anamnesis of changes) that lack features of melanoma. Complete excision should be considered in a lesion that shows significant changes on follow-up [5].

Automated diagnostic systems require no input by the clinician but rather report a likely diagnosis based on computer algorithms. There are many available software approved for medical use; however to date, the true benefits of these systems remain questionable [22].

1.2.1 Special Localizations

1.2.1.1 Face

In this site a specific *pseudo-network* with a broad mesh and holes, due to the numerous follicular and sweat glands openings, is generally seen in both melanocytic and non-melanocytic superficial lesions [23]. In lentigo maligna, in the first stage, hyperpigmented, asymmetric, follicular openings may be detected, with fine streaks, dots, and globules later developing around the follicles and creating the so-called annular-granular pattern along with the formation of rhomboidal structures; in the last stages, hyperpigmentation becomes homogeneous enough to obliterate follicular openings [5].

1.2.1.2 Palms and Soles

In these areas pigmentation is arranged through parallel lines that follow skin grooves [24]. Acral melanocytic nevi may show three different types of VD patterns: the *parallel-furrow pattern*, the *latticelike pattern*, and the *fibrillar pattern*. The *parallel-furrow pattern* is the most frequently observed: it shows linear pigmentation along the

Table 1.2 Common VD features of melanocytic lesions

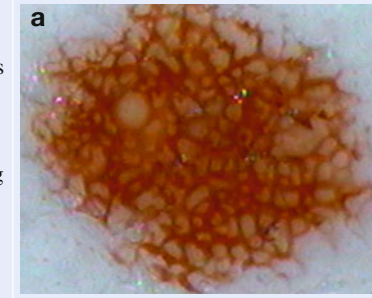
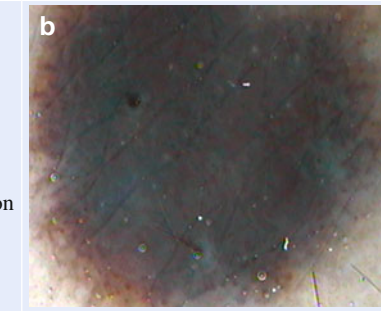
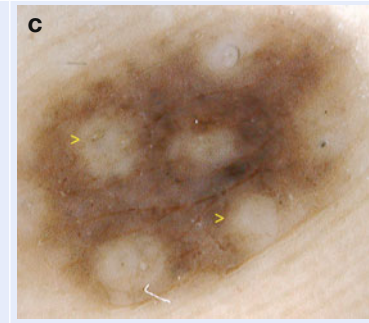
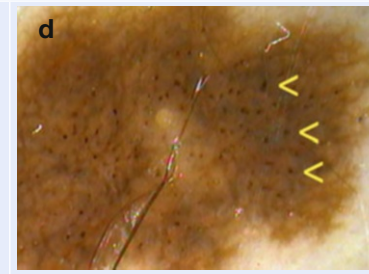
VD features	Description	Histopathologic correlation	
Pigment network	Grid of brownish lines over a tan background. It can be typical (regular, thin, narrow) or atypical (irregular, thick, wide) in benign and malignant melanocytic lesions, respectively	The lines correspond to melanin pigment contained in keratinocytes or in melanocytes outlining the pattern of the epidermal rete ridges, while the tan areas among them correspond to the dermal papillae tips	
Diffuse pigmentation	According to the localization of the melanin pigment within the skin, different colors can be seen. Even and uneven pigmentation is usually found in benign and malignant lesions	Melanin pigment localized within the epidermal stratum corneum appears black; in the lower epidermal layers light to dark brown; in the papillary dermis gray; pigmentation of the reticular dermis is steel blue	
Hypopigmentation	Diffuse or localized areas of decreased pigmentation, commonly observed in benign melanocytic lesions	Decreased melanin pigment	
Black dots	Small, round structures that may be regularly or irregularly distributed, respectively, in benign and malignant melanocytic lesions	Focal collections of melanin in the stratum corneum	

Table 1.2 (continued)

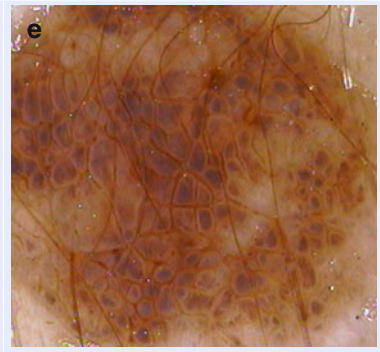
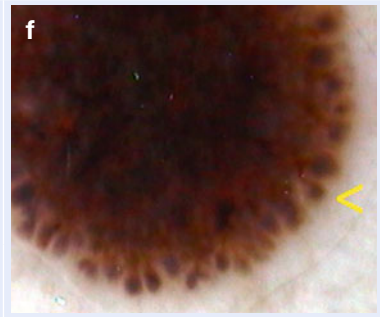
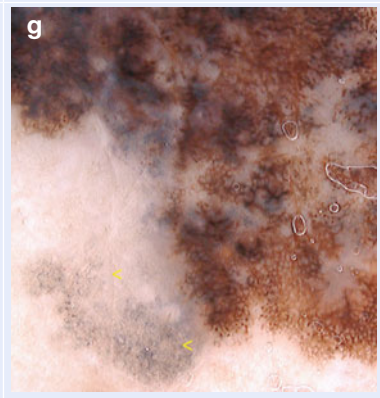
VD features	Description	Histopathologic correlation	
Brown globules	Round to oval, variously sized structures that show a regular or irregular distribution, respectively, in benign and malignant melanocytic lesions	Nests of melanin-containing melanocytes in the lower epidermis	
Streaks	This term comprises *radial streaming* and *pseudopods*, which irradiate from the lesion border: the former are narrow, closely arranged, parallel lines, the latter appear as digitiform extensions. Streaks may be regularly or irregularly distributed within both a pigmented Spitz nevus and a melanoma	Peripheral, confluent, and heavily pigmented junctional nests of melanocytes	
Regression	This term comprises *white scar-like depigmentation*, which corresponds to areas lighter than the normal skin, and the so-called *peppering*, which consists of speckled multiple blue-gray granules within a hypopigmented area. Regression is frequently observed in melanoma	Fibrosis and melanosis	
Blue-white veil	Irregular, ill-defined gray-blue to whitish-blue pigmentation dimming the underlying structures It is highly suggestive of melanoma	Acanthotic epidermis with focal hypergranulosis above sheets of melanophages and/or heavily pigmented melanocytes in the superficial dermis	

Table 1.3 Common VD features of non-melanocytic lesions

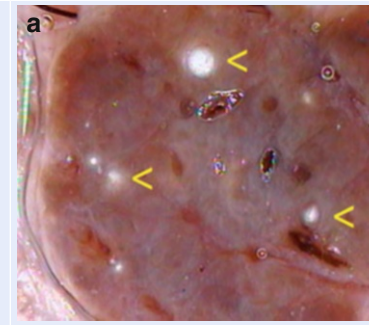
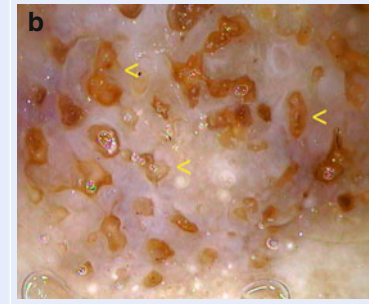
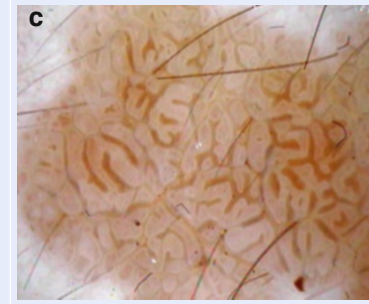
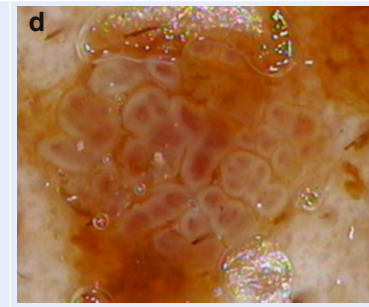
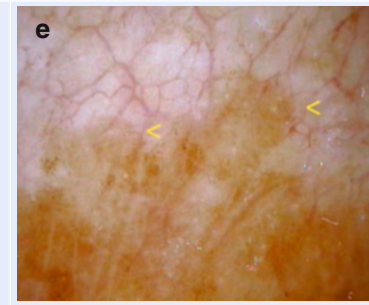
VD features	Description	Histopathologic correlation	
Milia-like cysts (horny pseudocysts)	Round luminescent whitish or yellowish structures. They are mainly observed in seborrheic keratoses	Small intraepithelial cysts filled with keratinized material	
Comedo-like openings	Round or oval-shaped yellow to brown areas. They are mainly observed in seborrhoeic keratoses, occasionally in papillomatous melanocytic nevi, rarely in melanoma	Keratin-filled invaginations of the epidermis	
Brain-like appearance	Irregular linear keratin-filled grooves (or sulci) alternating with yellowish to brownish ridges (or gyri). Typical of seborrheic keratoses	Keratin-filled invaginations of the epidermis	
Exophytic papillary structures	Dome-shaped formations. Observed in dermal nevi and in seborrheic keratoses	Pronounced papillomatosis	
Fingerprint-like structures	Light-brown, delicate, network-like configurations seen at the periphery of a lesion, producing a pattern that resembles fingerprints. They are typical of flat seborrheic keratoses	Thin elongated rete ridges that are heavily pigmented at the basal layer	

Table 1.3 (continued)

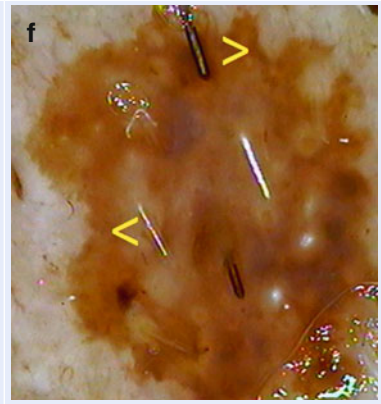
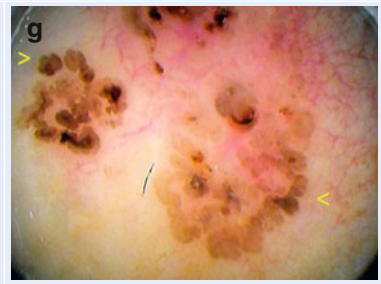
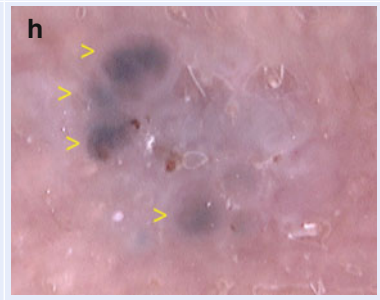
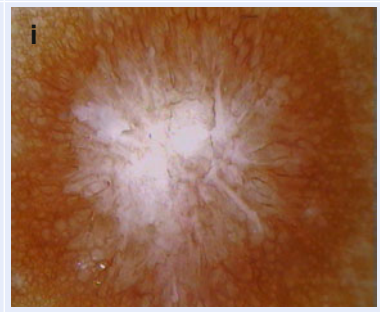
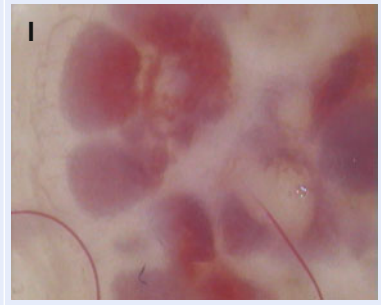
VD features	Description	Histopathologic correlation	
Moth-eaten border	Concave rim which has been compared to a moth-eaten garment. It is typical of flat seborrheic keratoses	Pigment distribution at the basal layer	
Leaflike areas	Brown-gray or gray-blue regions located at the lesion periphery, forming a leaflike pattern. Typical of basal cell carcinoma.	Clumps of pigmented basaloid cells	
	Radial projections meeting at a central axis are defined spoke-wheel areas		
Blue-gray globules and large blue-gray ovoid nests	Well-circumscribed, roundish to oval structures, of different sizes, not intimately connected to a pigmented tumor body. Suggestive of basal cell carcinoma	Pigmented basaloid cells	
Central white patch	Sharp circumscribed, round to oval, sometimes irregularly outlined, whitish area within the center of a pigmented lesion. Specific for dermatofibroma	Epidermal hyperplasia overlying a variable amount of dermal fibrosis	
Red-blue areas (red lacunas or red lagoons)	Roundish or oval structures with a reddish or red-bluish coloration. Typical of angiomas. They may acquire a deep blue to black color after thrombosis	Widened vascular lacunae located in the superficial dermis	

Table 1.4 Common vascular structures in skin lesions

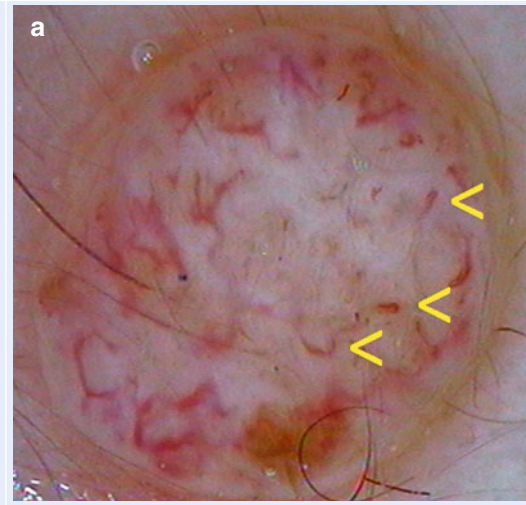
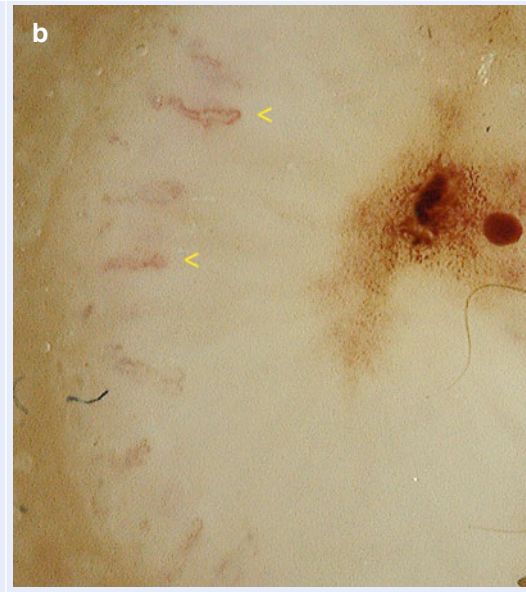
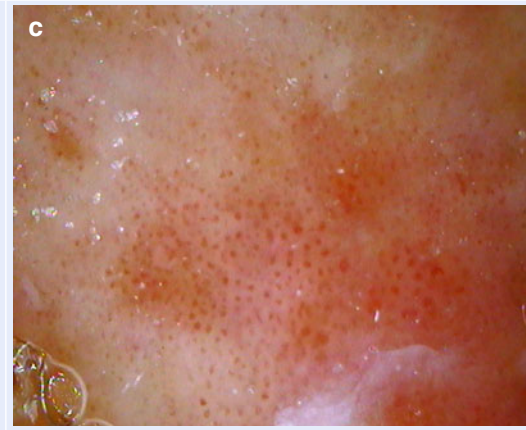
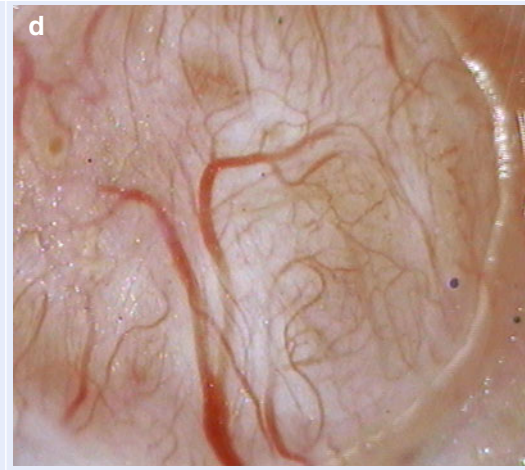
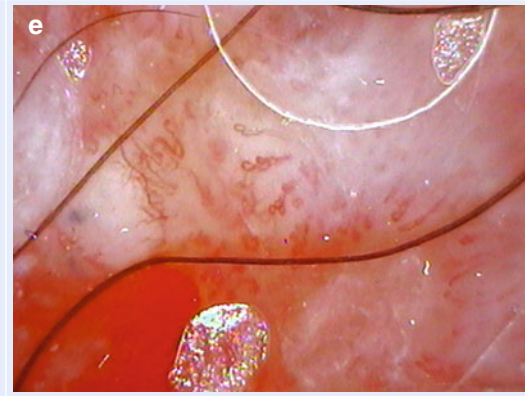
Vascular structure	Description	
Comma-like	Short, strongly curved blood vessels predominantly seen in dermal nevi	
Hairpin-like	Long capillary loops which may be seen in melanoma, keratoacanthoma and seborrheic keratoses	
Dotted	Small pinpoint vessels corresponding to short capillary loops, which are commonly seen in all types of tumors, including melanoma and Bowen's disease	

Table 1.4 (continued)

Vascular structure	Description	
Treelike	Thick and arborized structures commonly observed in basal cell carcinoma	
Linear irregular	Predominantly seen in melanoma	

grooves between the skin markings and two linear lines along both sides of each sulcus; single or double dotted lines along the sulci may be present as variants. The *latticelike pattern* shows a linear pigmentation which follows and crosses the surface sulci. The *fibrillar pattern* is characterized by fine fibrillar pigmentation running in a slanting direction to the skin markings. In situ acral melanoma shows the so-called *parallel ridge pattern*, a diffuse and fine reticular, irregularly shaped pigmentation that follows the papillary tips [5]; however, some benign acral lesions may show parallel ridge pattern on VD [25].

1.2.1.3 Other Sites

The use of VD for pigmented lesions of the nails or mucous membranes (both oral and genital) has been significantly less investigated [26–28]. There is a need to intensify research, which would result in creating diagnostic algorithms, useful for early detection of melanoma.

1.3 Nonpigmented Skin Lesions

VD may be useful for the diagnosis of several nonpigmented skin proliferations, showing in some cases specific features. In those cases characterized by indicative but not specific features, VD may help to rule out clinically similar disorders that do not show that pattern.

1.3.1 Sebaceous Hyperplasia

VD features: Central aggregation of white-yellowish globules (*cumulus sign*) surrounded by a crown of vessels (Fig. 1.2). Occasionally, the

Table 1.5 Melanocytic lesions and VD correlations

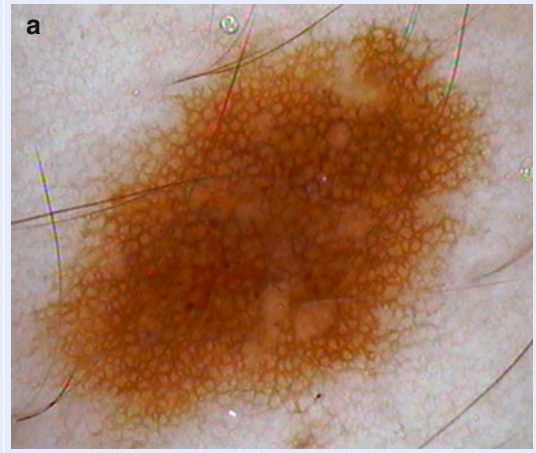
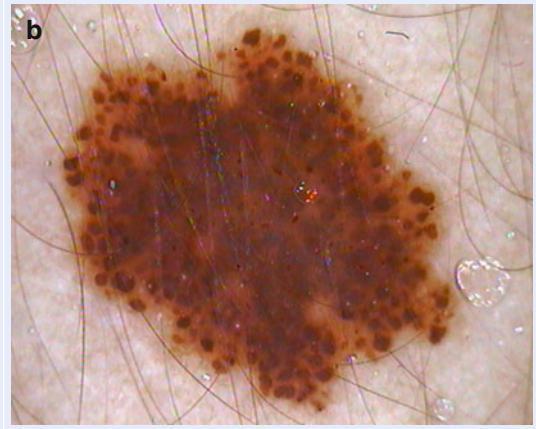
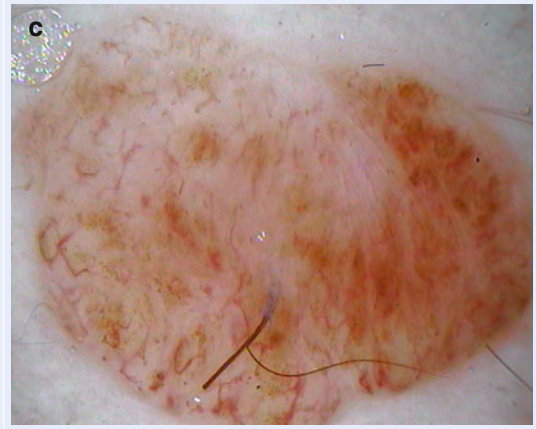
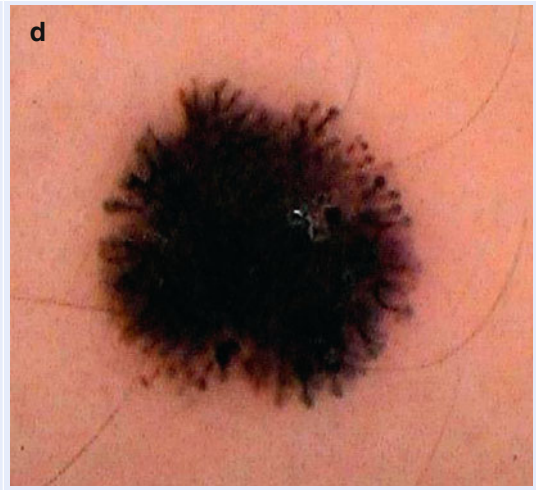
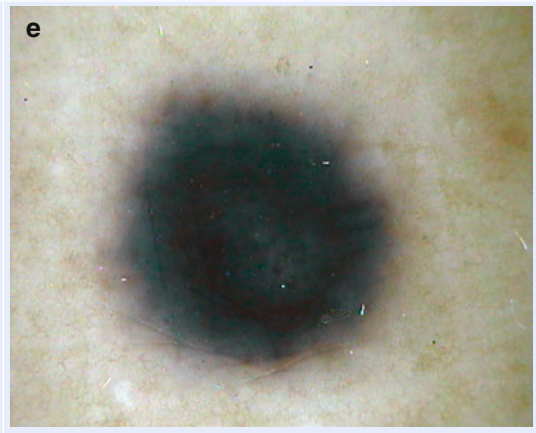
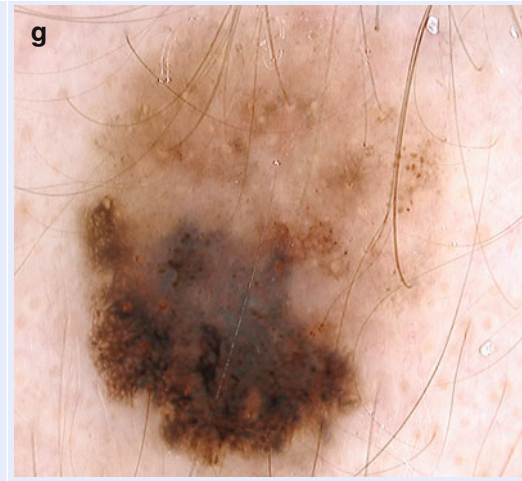
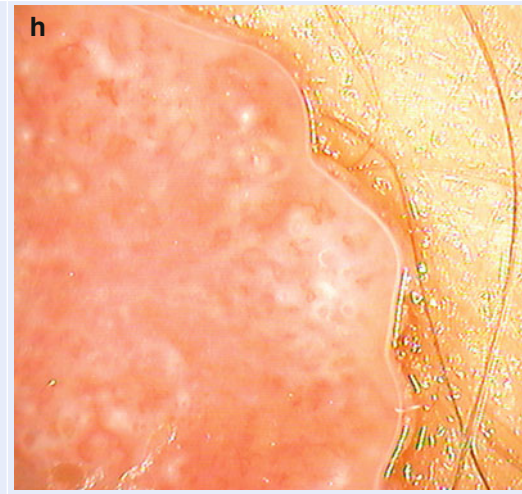
Melanocytic lesion	VD features	
Junctional melanocytic nevus	Regular, delicate pigment network that gradually fades at its periphery. In its central portion, multiple black dots or a uniform dark pigmentation may be present	
Compound melanocytic nevus	Pigment network and/or diffuse brown pigmentation. It also exhibits regularly distributed brown globules	
Dermal melanocytic nevus	Brown globules varying in size and color, sometimes arranged to create a "cobblestone" effect. Comma-like vessels are commonly observed	

Table 1.5 (continued)

Melanocytic lesion	VD features	
Pigmented Spitz nevus	Characteristic starburst pattern formed by a prominent gray-blue to black diffuse pigmentation and by streaks radially and regularly located along the periphery. In its center, a reticular black-whitish to blue-whitish veil, called reticular depigmentation, may be present. The starburst pattern may rarely be seen also in melanoma; thus, in adult patients, a biopsy should be performed when such spitzoid features are detected by VD	
Blue nevus	Homogeneous blue pigmentation with complete absence of other findings. Multiple areas of hypopigmentation corresponding to fibrosis may be observed	
Melanoma in situ and early invasive melanomas	Diffuse pigmentation irregular in color and/or distribution, atypical pigment network with wide and irregular meshes and thick lines ending abruptly at the periphery, dots or globules variously sized and haphazardly distributed, irregularly dispersed streaks	

(continued)

Table 1.5 (continued)

Melanocytic lesion	VD features	
Intermediate and thick melanomas	The previous findings are associated with a blue-whitish veil and, frequently, with dotted, linear irregular, and/or hairpin vessels. Regression may also be present and, if extensive, should always prompt biopsy, despite the presence of other VD criteria, to avoid missing a melanoma	
Amelanotic melanoma	Presence of polymorphous vessels, which may be evident as dotted, hairpin, and/or linear irregular. Moreover, milky-red globules or milky-red areas which appear as localized or diffuse areas of reddish-white color may be seen; these findings are thought to represent highly vascularized amelanotic tumor cell complexes	

ostium of the gland is visible as a small crater or umbilication in the middle of these yellowish structures (*bonbon toffee sign*) [29, 30].

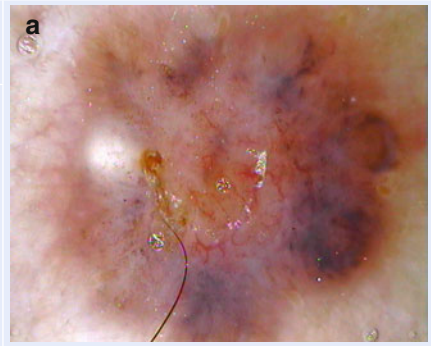
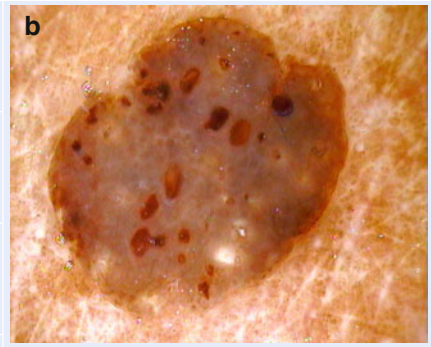
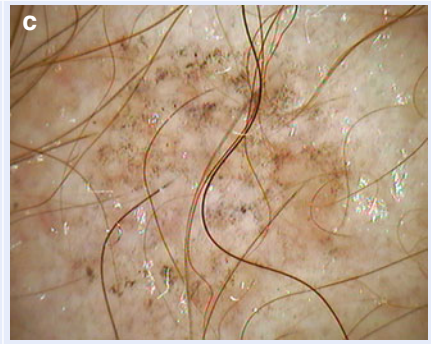
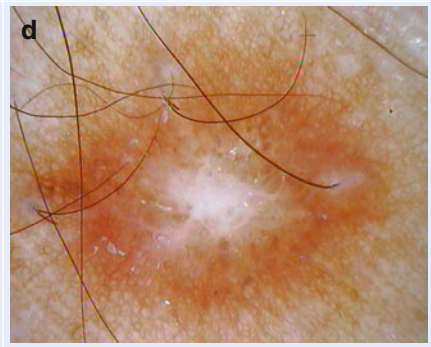
1.3.2 Pyogenic Granuloma

VD features: Typical pattern characterized by a red to dark pink homogeneous area, corresponding to proliferating vessels, surrounded by a white collarette corresponding to the hyperplastic epithelium. Additional findings include white lines intersecting the lesion (*white rail*) (Fig. 1.3), histologically corresponding to fibrous septa that surround the capillary tufts or lobules, and ulceration [31].

1.3.3 Clear Cell Acanthoma

VD features: At low magnification (×20 to ×50), homogeneous, symmetrical dotted vessels throughout the entire lesion arranged either in a netlike pattern or as pearls on a line. At higher

Table 1.6 Non-melanocytic lesions and VD correlations

Non-melanocytic lesion	VD features	
Basal cell carcinoma	Leaflike areas, spoke-wheel areas, blue-gray globules and/or large blue-gray ovoid nests.	
	The presence of treelike vessels and/or ulcerations is also typical	
Seborrheic keratosis	Milia-like cysts and comedo-like openings on a background varying from opaque light brown to dark brown or black.	
	A pronounced black pigmentation camouflaging the pathognomonic features may be seen (melanoacanthoma).	
	Other morphological findings that sometimes may be observed include a brain-like appearance and exophytic papillary structures.	
	Some flat seborrhoeic keratoses (also known as solar lentigines) may show either a fingerprint-like pattern or a moth-eaten border	
Lichen planus-like keratosis	Brown-gray and blue-gray granular pattern	
Dermatofibroma	Central white patch surrounded by a delicate, regular, usually light-brown pigment network. Sometimes within the central patch several small round to oval globules of light-brown coloration may be found	

(continued)