DERMATOSCOPIC PATTERN VARIABILITY IN BASAL CELL CARCINOMA – IMPLICATIONS IN DIAGNOSIS, PREOPERATIVE ASSESSMENT, AND TUMOR MANAGEMENT

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Abstract

Basal cell carcinoma is a slow growing non-melanoma skin cancer appearing as a non-healing, painless, and sometimes pruriginous sore, usually on sun-exposed areas. Although it rarely metastasizes, BCC diagnosis and treatment should not be delayed due to its local invasive potential. Currently, dermatoscopy is a well propagated and commonly employed tool in clinical practice, providing a fast and handy approach to clinical diagnosis, without the significant financial costs associated with other more sophisticated diagnostic means. Since the very first dermatoscopic descriptions of basal cell carcinoma, the list of dermatoscopic diagnostic criteria has been updated and renewed numerous times. Dermatoscopy significantly augments basal cell carcinoma detection by its capability of discriminating it from other skin lesions and inflammatory skin conditions. Moreover, current evidence suggests that this noninvasive, real-time imaging technique is also valuable in tumor management, seeing that it provides additional information related to histopathological subtype, presence or lack of pigmentation, lateral tumor extension, and tumor response to non-surgical treatments. In this paper, we aim to summarize time-honored as well as current knowledge on the value of dermatoscopy in the diagnosis, classification, and treatment of basal cell carcinoma.

Keywords:
- dermatoscopy;
- carcinoma;
- basal cell;
- non-melanoma skin cancer;
- pigmentation;
- non-invasive diagnosis.

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Introduction

Basal cell carcinoma (BCC) is a slow growing non-melanoma skin cancer (NMSC) that arises from the epidermal basal cells and exhibits an irregular infiltration pattern (1).

The clinical appearance of basal cell carcinoma is that of a non-healing, painless, and sometimes pruriginous sore, usually arising on sun-exposed areas such as the face, head, neck and back of the hands. However, this tumor has multiple clini-
cal representations as a macule, papule, plaque or nodule, coloured in either pink, brown or red (2). It is precisely this clinical variability which leads clinicians confronted with BCC diagnosis to consider a variety of differential diagnoses which widely vary, ranging from atypical nevi to melanoma.

One of the most viable hypotheses explaining the occurrence of BCC is linked to long term ultraviolet radiation (UVR) damage, also known as cumulative skin damage. At the same time, the risk of BCC development is significantly increased by exposure to chemicals including arsenic, insecticides, herbicides, pesticides, and radiotherapy (3, 4). Epidemiologic data emphasise that, despite awareness campaigns and sun-protective measures, there is an increasing global BCC incidence, especially in middle-aged groups, suggesting that BCC has become a serious public health concern (4, 5). Consequently, in many countries the treatment costs of this common skin cancer have become a true financial burden.

Unlike other types of cancer, BCC rarely metastasizes (6). Nonetheless, diagnosis and treatment should not be delayed due to its local invasive potential (7). Investigation methods such as dermoscopy, high-frequency ultrasound, reflectance confocal microscopy, optical coherence tomography, and proteomic techniques have proved to be very accurate in diagnosing and classifying tumour type and, to some extent, predicting tumor behaviour (8-13). Nowadays, dermatoscopy is the most commonly propagated and employed tool in clinical practice, as it provides a fast and handy approach without the significant financial costs associated with other more sophisticated diagnostic means. Also known as skin surface microscopy, epiluminescence microscopy, or incident light microscopy, dermatoscopy is an in vivo, non-invasive, real-time investigation. It allows for the examination of skin morphologic features that are not visible to the naked eye, being useful in both pigmented and nonpigmented lesions for which the clinical diagnosis is uncertain. Dermatoscopy can also provide an early differentiation between malignant and benign cutaneous lesions (14).

1. Dermatoscopic diagnosis of BCC

Although dermatoscopy has proved its efficacy in differentiating BCC from other tumors with a sensitivity of 95-97% and a specificity of 87-96%, depending on the subtype of BCC (14), the list of dermatoscopic features of BCC has been updated and reviewed multiple times (15).

The current available literature reveals that studies in dermatoscopy have mainly focused on pigmented lesions (16-20). Miller et al. describe the main dermatoscopic criteria for pigmented BCC as the presence of dermo-epidermal melanin deposit in the form of concentric structures, brown-black globules, and pseudopods (21). Nevertheless, some authors suggest that pigmented BCC should no longer be considered a clinical variant, due to the possible presence of pigmentation in all BCC subtypes (22).

In the year 2000, Menzies et al. (18) introduced the classic dermoscopic features for BCC, which are based on the absence of a pigmented network. They include at least one of the following patterns: small ulcerations in the absence of recent trauma, multiple blue-gray globules, maple leaf-like areas, large blue-gray ovoid nests, spoke-wheel areas, arborizing telangiectasia, truncated vessels, and hypopigmented areas (Figure 1). This set of criteria can be invaluable to the clinician in the initial evaluation of lesions, prior to performing a cutaneous biopsy.

Later, in 2008, Scalvenzi et al. (23) added other important criteria such as shiny white to red areas, short fine telangiectasias, and erosions. In 2010, Altamura et al. (24) helped in completing the set of criteria by presenting two more elements: concentric structures, and multiple, in-focus, blue-gray dots. A study based on the dermatoscopic investigation of 92 non-pigmented BCCs reported that the most frequent features present were arborizing blood vessels (black arrowheads), fine arborizing vessels (thin black arrow), and ulceration (white asterisk) in a nodular BCC; Globules (orange thin arrows), blue-gray ovoid nest (red thin arrow), and ulceration covered by hematic crust (white asterisk) in a pigmented BCC; Black dots and dotted vessels (white arrowheads), leaf-like structures (white thin arrow), and small ulceration (white asterisk); Blue-gray ovoid nest (red arrow), leaf-like areas (white thin arrow), a central red-white structureless area (black “T”), and small ulceration covered by hematic crusts (white asterisks) in a pigmented BCC; Blue-gray ovoid nests (red arrows) and a pinkish astructural area (black “T”); Spoke-wheel areas (red arrowheads) in a superficial, pigmented BCC.
telangiectasia, followed by ulceration, short fine superficial telangiectasia, non-arborizing vessels, and multiple small erosions (25).

To simplify the dermatoscopic diagnosis of BCC, Stoecker et al. (26) introduced the B.A.S.A.L acronym, aimed to encompass all these features: Blue-gray ovoids and globules, Arborizing telangiectasia, Spoke-wheel structures, Atraumatic ulcerations and Leaf-like structures (Figure 1).

2. Dermatoscopic determination of pigmentation in BCC

Dermatoscopy is a very powerful tool for assessing the presence or lack of pigmentation. The consensus net meeting on dermoscopy of 2000 established a series of dermatoscopic criteria significant for the diagnosis of pigmented BCCs. These criteria include ulcerations, maple leaf-like areas, large blue-gray ovoid nests, multiple blue-gray globules, spoke-wheel areas, and arborizing telangiectasia (16). The dermatoscopic analysis of BCC has since brought to light other features such as irregular depigmentation, black dots, irregular borders and surfaces, and whitish veil, elements usually encountered in melanoma.

Certain studies (27) have emphasized that clinically undetectable pigmentation occurs in almost 30% of macroscopically non-pigmented BCC, which could mislead clinicians to misjudge the diagnosis and, as a consequence, apply an ineffective treatment. For example, Enei et al. (28) reported an intriguing case of “radial streaking” in a superficial multicentric BCC. Upon dermatoscopic examination, the authors found brown to black pigmented streaks, irregularly and centrifugally arranged, localized at the bottom of an ulceration, associated with grey-brown elongated structures. Histopathology in this case revealed a pigmented multicentric superficial BCC with melanophages in the upper dermis. Another challenging case was reported by Belluci et al. (29), who described an association of yellowish structures and classic BCC features. In the literature, yellowish structures encompass milia-like cysts (MLCs) and yellow lobular-like structures, in this case the patient having developed a BCC on top of a nevus sebaceous of Jadassohn. Although Menzies et al. (17) estimated a 10% sensitivity for MLCs in pigmented BCCs, further data is needed.

3. Dermatoscopy in the pre-operative histopathologic classification of BCC

Currently, a skin biopsy is necessary to evaluate histopathological features that can guide the management and treatment of a BCC. Common features for all BCC histopathological subtypes are basaloid cells with pale cytoplasm surrounding round nuclei with granular chromatin; cell layers in the periphery are arranged in palisade, and the surrounding stroma is usually separated by slits or clefts. This so-called "stromal retraction" was once considered to be an artefact of paraffin embedment. Nevertheless, newer in vivo technologies such as optical coherence tomography and reflectance confocal microscopy also reveal this detail, leading researchers to believe that this peritumoral clefing is due to collagen contraction and/or cell adhesion alteration, and peritumoral mucin deposition. Moreover, intercellular bridges may be present (13, 16-20). There have been numerous attempts at classifying the histopathological subtypes of BCC. In 1978, Wade and Ackerman managed to categorize 26 subtypes of BCC, which was the highest number in medical literature (21). Later, in 1996, the World Health Organization (WHO) presented a classification system of the histopathological differentiation of BCC subtypes which is more realistic (25). According to most classifications, there are main types, subtypes and mixed types of BCC (22, 25, 26). The four main subtypes of BCC, according to WHO, are nodular, micronodular, superficial, and infiltrative.

It is not for a lack of trying (see Table 1) that, to this day, studies have not established a consistent and reliable connection between dermatoscopic criteria and BCC histopathological subtypes. This was investigated for the first time in 1989, by Soyer et al. (7), who introduced the histological counterparts of several dermatoscopic parameters, such as pigment network, black dots and irregular extension. Later, in 1993, Yadav et al. (8) added features such as brown globules, hypopigmented areas, white and gray-blue areas, and whitish veil. Still, all this terminology was reviewed in the Consensus Meetings on Dermoscopy in 2016 (30). In a relatively recent article, Menzies et al. associated several dermatoscopic observations with histopathologic findings, albeit only for pigmented BCC (18). This matter was revisited in 2002 by Ferrara et al., who pointed out that the dermatoscopic features of pigmented BCC, such as multiple gray globules, can be correlated with pigmented solid aggregations of basaloid cells in the papillary dermis (31).

Betti et al. (37) examined the accuracy of dermatoscopy in discerning superficial BCC from other histopathological subtypes. This discrimination is especially relevant for clinicians, due to the inappropriate choice of treatment in the case of mistaking a nodular or infiltrative BCC for a superficial one. Superficial BCC is dermatoscopically characterized by short fine telangiectasia, small erosions, maple-leaf like and spoke wheel areas, whereas nodular BCC is characterized by blue-gray ovoid nests, arborizing vessels and large ulcerations. The presence of blue-gray ovoid nests usually excludes superficial BCC. The more aggressive histopatho-
logical subtype, infiltrative BCC, has a dermatoscopic pattern generally consisting of arborizing smaller caliber vessels and shiny white-red areas (38).

Recent studies (39-42) have uncovered a rare epithelial neoplasm, basosquamous carcinoma (BSC), which is characterized by features of both basal cell and squamous cell carcinoma (SCC). Its clinical

<table>
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<tr>
<th>Dermatoscopic elements</th>
<th>Histopathological correspondent</th>
<th>Authors</th>
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<tr>
<td>Arborizing vessels (linear straight or linear serpentine) – in focus appearance</td>
<td>Vessels limited to the superficial dermis</td>
<td>Verduzco-Martínez AP, <em>et al.</em> (2013) (32)</td>
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<td>Semi translucency</td>
<td>Superficial basaloid tumor conglomerates in the presence of a diminished epidermal thickness and a thinned collagen layer</td>
<td>Stoecker WV, <em>et al.</em> (2009) (33)</td>
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<tr>
<td>Fine arborizing vessels</td>
<td>Vessels limited to the superficial dermis</td>
<td>Verduzco-Martínez AP, <em>et al.</em> (2013) (32)</td>
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<td>Globules – brown or black, diameter larger than 0.1 mm</td>
<td>Pigmented tumor islands</td>
<td>Menzies SW, <em>et al.</em> (2000) (18)</td>
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<tr>
<td>Central red-white, translucent to opaque structureless areas</td>
<td>Sparse nests of basaloid tumor cells at the dermo-epidermal junction, with the predominance of loose fibrous stroma interlaced by a downward proliferation of numerous, interconnecting epithelial strands</td>
<td>Rossiello L, <em>et al.</em> (2006) (34); Lallas A, <em>et al.</em> (2014) (15)</td>
</tr>
<tr>
<td>Multiple small ulcerations</td>
<td>Multiple areas of epidermal and/or superficial dermal loss ± hematogenous crusts</td>
<td>Verduzco-Martínez AP, <em>et al.</em> (2013) (32)</td>
</tr>
<tr>
<td>Spoke-wheel areas – radial projections, light-brown, occasionally blue or gray, radiating from darker central axis, typically located at the border of a structureless red to white area</td>
<td>Tumor cell aggregates arranged in cords located in the papillary and/or reticular dermis, connected in multiple points to the base of the epidermis, growing radially from a central pigmented core, pigmented melanophages in the fibrous stroma.</td>
<td>Stephens A, <em>et al.</em> (2013) (36); Lallas A, <em>et al.</em> (2014) (15)</td>
</tr>
<tr>
<td>Concentric structures – irregular, globular structures of various colors and a darker central area; variation or the “precursors” of the spoke-wheel pattern</td>
<td>Small tumor islands connected to the epidermis, exhibiting centrally located pigmentation</td>
<td>Lallas A, <em>et al.</em> (2014) (15)</td>
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<tr>
<td>Dotted vessels and whitish streaks (chrysalis pattern) – orthogonal short and thick crossing lines seen with polarized dermatoscopy</td>
<td>Collagenous stroma and dermal fibrosis</td>
<td>Lallas A, <em>et al.</em> (2014) (15)</td>
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</table>
appearance is nonspecific, and as such, it can be easily mistaken for any other malignant skin lesion. Upon dermatoscopic examination, BSC can present with elements common to both BCC and SCC (43) such as ulcerations, blue-gray ovoid nests, and unfocused arborizing vessels. Histologically, it also presents areas of both BCC and SCC with a transition zone between them. For example, BCC areas have uniform peripheral palisading cells, with mitoses and fibroblast proliferation, while SCC areas have polygonal squamoid cells with cytoplasmic keratinization, large nuclei, and frequent mitoses. Because of its metastasis incidence which is higher than either BCC or SCC alone, early detection and surgical removal are crucial.

Another uncommon type of BCC is nevoid BCC, which is mainly found in patients diagnosed with Gorlin-Goltz syndrome. Dermatoscopically, this particular BCC type generally presents with brown pigmentation, blue-gray globules, and arborizing vessels (44).

All things considered, identifying more consistent links between the diversity and the complexity of dermatoscopic and histological features of BCC remains a major challenge in need of further investigation.

4. Dermatoscopy in BCC management

Besides being viewed as one of the most valuable investigation methods for the early diagnosis of basal cell carcinoma, dermatoscopy also plays an essential role in tumor management.

According to current guidelines, the management of BCC is guided by several factors including histopathological subtype, anatomical location, tumor depth, the presence of ulceration or pigmentation, vascularization, and the presence of residual disease or recurrence (4, 38, 45).

Therefore, non-surgical approaches are established as first line treatment for superficial BCC, while surgical excision represents the optimal choice for nodular BCC. Furthermore, Mohs micrographic surgery is recommended in more aggressive BCC subtypes, such as infiltrative, sclerodermiform or micronodular BCCs (46).

As non-surgical treatments of BCC, imiquimod and photodynamic therapy (PDT) are considered to be first choices in superficial BCCs (47, 48) and, under certain circumstances, can even be used for nodular BCCs. The presence of pigmentation plays an important role in choosing PDT therapy, because randomized controlled trials have assessed that pigmented BCCs exhibit poor response rates to PDT when compared to non-pigmented variants (49). The key in surgical excision is represented by the excision margins, defined by Carducci et al. (50) as the absence of BCC dermatoscopic criteria. To avoid the unnecessary removal of healthy skin, Mun et al. (51) presented a theory based on the caliber and configuration of the blood vessels, considering that these are important features in defining excision margins. The study put forth the idea that arborizing vessels and superficial fine telangiectasia may extend to the perilesional skin, as they are feeding the tumour and are not necessarily part of it. Following the guidelines of standard surgical excision the lateral excision margins range from 3 to 10 mm, according to tumor size, site, borders, and previous treatments (46, 52-54). However, in a previous study (46), in which 200 BCCs were surgically removed with a 2 mm margin, the histological examination assessed that 98.5% of cases were completely excised. This study highlighted that overestimation of the tumor can lead to unnecessary aesthetic issues. In contrast, Sartore et al. (55) emphasized that 6.5-16.9% of BCCs are incompletely excised, which can change the structure of the tumor and, consequently, induce a recurrence with a faster growing rate.

To provide a low recurrence rate and an ideal separation from the healthy adjacent tissue, Mohs micrographic surgery is preferred for the more aggressive BCC subtypes, and also for lower risk variants situated in aesthetically important regions (face, neck, and anterior chest wall). Mohs excisions are step-wise and have the advantages of intraoperative monitoring and histological control. Although it may seem like the best choice for the treatment of BCC given the association between radical excision and healthy tissue preservation, Mohs surgery is limited by operator expertise, time, financial cost, and infrastructure (56).

Conclusion

Over time, dermatoscopy has transitioned from a second-level investigation method employed for the evaluation of clinically equivocal skin lesions to an indispensable part of the clinical examination process. Dermatoscopic criteria for non-melanoma skin cancer detection have been continuously revised and improved through numerous studies and consensus meetings, to the point where even atypical and rarely observed patterns have been described and documented. In the case of basal cell carcinoma, dermatoscopy does not only refine the clinical differential diagnosis, but it also provides additional information, essential for choosing the appropriate management course, and aids in the management of this non-melanoma skin cancer.

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