

CLINICAL REPORT

High Magnification Digital Dermoscopy of Basal Cell Carcinoma: A Single-centre Study on 400 cases

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The aim of this study was to assess the frequency of classic dermoscopic basal cell carcinoma (BCC) features and the sensitivity of new descriptors, such as light brown nests (homogeneous and structured) only visible employing a high magnification digital videomicroscope. A retrospective analysis of 2,024 highly magnified digital images referring to 400 BCCs was performed by 3 independent observers, who assessed 11 classic BCC descriptors and the new ones. Light brown nests were detected in 40.5% of BCCs. Homogeneous ones were observable in 17.8%, and structured nests in 32.8%. Light brown nests were visible in 14.3% of non-pigmented lesions, whereas in the pigmented groups these were observed in 42–54% of the cases. We suggest that brown nests described in this study may improve early recognition of superficial BCCs and of non-pigmented or slightly pigmented ones that may lack classic dermoscopic patterns. Key words: videomicroscopy; basal cell carcinoma; dermoscopy; light brown nests; histopathological subtypes.

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Basal cell carcinoma (BCC) represents the most frequent skin cancer in the white population, with a global incidence which is increasing worldwide, particularly in younger age groups (1). The differentiation between BCC and other skin lesions is of great importance, since serious morbidity may result from an undiagnosed tumour. Upon clinical inspection the diagnosis of nodular lesions can be easily performed in most cases. However, the differential diagnosis for other BCC subtypes may be broad and may require dermoscopic examination, which has shown to improve the diagnosis of both melanocytic and non-melanocytic lesions, including BCC, with respect to naked eye assessment (2–5).

The dermoscopic aspects of pigmented BCC have been well defined by Menzies et al. (6) who proposed to base the diagnosis of BCC on the absence of pigment network and the presence of at least one of 6 positive

morphological features, including arborising “tree-like” vessels, ulceration, multiple blue-gray globules, large blue-gray ovoid nests, leaf-like areas and spoke wheel areas. Additional features, such as short fine telangiectasia and multiple small erosions located on a shiny white to red structureless background have been introduced as dermoscopic characteristics of superficial BCC, and should be taken into account along with the recently described concentric structures and multiple in focus blue-gray dots (7–11).

The literature reports that, employing these criteria, specificity and sensitivity of BCC diagnoses are high. However, some dermoscopic aspects of BCC are strictly instrument-dependent. Recently described features such as white shiny streaks, chrysalis structures and the rosette sign are only visible with polarised dermoscopy and do not apply to immersion contact dermoscopy (12–17).

Moreover, the recognition of many BCC characteristics is magnification dependent, and descriptors based on the assessment of size, e.g. dots/globules, globules/nests or arborising vessels/short fine telangiectasia, may potentially show great inter-observer variations. Finally, most studies are based on non-homogeneous BCC dermoscopic image series, acquired by different instrumentation and magnification (9, 10).

The aim of the present study was to assess the sensitivity of classic BCC features and of new descriptors on a large homogeneous single-centre database, collected by employing an often utilised high-magnification digital videomicroscope. We also wanted to evaluate the distribution of different dermoscopic features in different histological BCC subtypes and correlate these data with clinical features including patients' gender, age and location of the lesions.

MATERIALS AND METHODS

The study was performed according to the directives of the Local Ethics Committee in accordance with ethical standards on human experimentation and with the Helsinki Declaration.

The database belongs to the Department of Dermatology, University of Modena and Reggio Emilia, Italy, and comprises 400 BCCs of head-neck, trunk and limbs, collected during the period 2007–2011. A retrospective analysis of 2,024 digital dermoscopic images was performed by 3 independent observers, who assessed the presence/absence of 11 BCC descriptors on

50- and 70-fold magnified images. Dermoscopic images had been previously recorded by means of a non-polarised digital epiluminescence microscope (FotoFinder, TeachScreen software GmbH, Bad Birnbach, Germany). The instrument and the calibration method have already been described elsewhere (16). Images were presented to the observers, who scored them without knowledge of histopathological BCC subtype and any clinical data of the patients and lesions. The following criteria specific for BCC were considered: arborising vessels; (6) large blue/gray ovoid nests; (6) ulceration; (6) multiple blue/gray globules; (6) maple-leaflike areas; (6) spoke-wheel areas; (6) short fine telangiectasia; (7) multiple small erosions; (7) concentric structures, (10) and shiny white to red areas (7).

Prior to evaluations, the first 50 cases were contemporarily observed by the dermatoscopists and collegially discussed in order to reach a consensus on the parameters to be employed. The feature "multiple in-focus blue-gray dots", described by Altamura et al. (10) was not evaluated, since it was impossible to attain an agreement among the observers. Dots of any type were assessed, irrespective of their colour. Moreover, new features of BCC were introduced. In some highly magnified images (50- and 70-fold), "homogeneous light brown nests" and "structured light brown nests" were observed (Fig. 1). Whereas the former appear as homogeneously light brown globules, the latter consist of light brown globules including either gray-blue structures or aggregated dots or commas or both.

Subsequently, the inter-rater reliability of dermoscopic features was assessed.

For data analysis, the histopathologic subtypes were separated into 4 categories: superficial, nodular, infiltrative BCCs and lesions with combined histopathologic patterns (combined BCCs). Moreover, lesions were classified according to the extension of dermoscopic pigmentation at a 20-fold magnification as: non-pigmented BCCs; lightly pigmented BCCs, showing pigmented areas involving less than 30% of the lesion surface; pigmented BCCs, displaying pigmented areas involving 30–70% of the lesion surface; and heavily pigmented BCCs, characterised by the presence of pigmentation on more than 70% of their surface.

Demographic data such as age, sex, and anatomic site of the lesions, were also collected for each patient and correlated to dermoscopic parameters.

Statistics

Statistical analysis was carried out using the Statistical Package for the Social Science (SPSS, Chicago, USA), Version 12.0 for Windows®. Differences between the frequencies of dermoscopic descriptors of histopathological and clinical subtypes were assessed by means of the Chi-square test of independence.

The agreement between ratings made by 3 observers on specific patterns of BCC (inter-rater reliability) was estimated using Cohen kappa statistics with 95% confidence intervals. A p -value < 0.05 was considered significant.

RESULTS

A total number of 2,024 dermoscopic images referring to 400 BCCs were taken from 335 individuals, including 170 men (50.8%) and 165 women (49.3%) patients with a mean age of 62.4 ± 15.3 years. Most nodular BCCs were observed in men (56.7%), whereas most superficial BCCs and combined BCCs (54.6 and 63.2, respectively) were observed in women. Individual lesions were located on head/neck in 38.0%, trunk in 47.3% and limbs in 14.8%. Lesions included 208 nodular, 119 superficial, 54 infiltrative and 19 combined BCCs. Nodular and infiltrative BCCs were located predominantly on head/neck, whereas superficial ones were more frequently located on the trunk (Table I). Out of 400 BCCs, 84 were non-pigmented, 111 lightly pigmented, 100 pigmented and 105 heavily pigmented (Table II).

Table I shows the frequency of BCC features in the whole BCC population and in different histological BCC subtypes. Considering all BCCs, the most frequent feature was arborising vessels, followed by short fine telangiectasia and shiny white to red areas. The prevalence of vascular features differed according

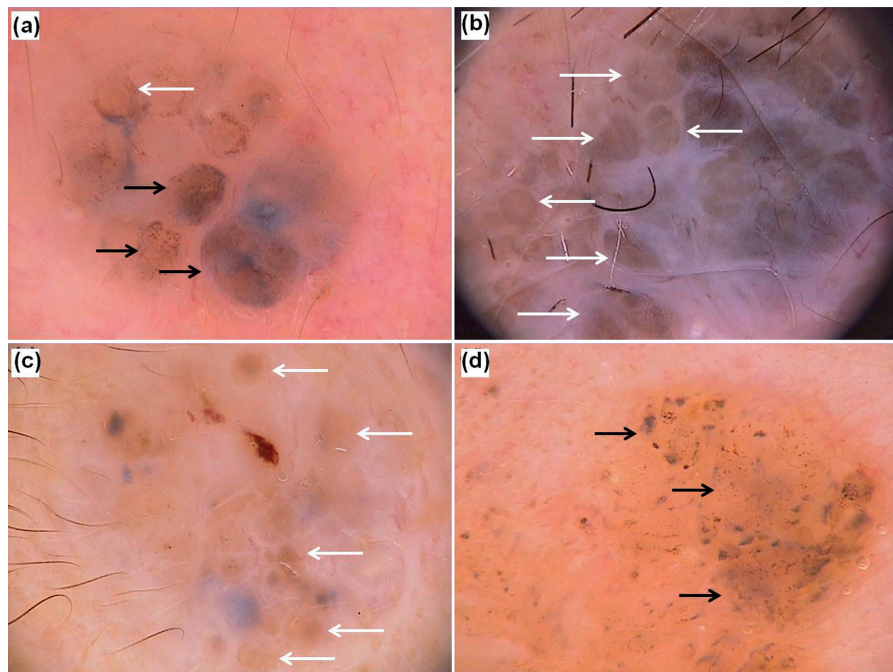


Fig. 1. Light brown nests. 50-fold magnified BCCs (a); 20 fold magnification (b); 70-fold magnified BCCs (c, d). Numerous structured light brown nests (black arrows) and homogeneous light brown nests (white arrows).

Table I. Frequency (%) of localisation and dermoscopic features according to histologic subtype and reproducibility (κ) values

	Nodular (n=208) %	Superficial (n=119) %	Infiltrative (n=54) %	Combined (n=19) %	Total (n=400) %	κ 1 vs 2	κ 1 vs 3	κ 2 vs 3
Head/neck	48.1 ^a p=0.000	10.9	59.3 ^a p=0.000	36.8 ^a p=0.009	38.0			
Trunk	40.3 ^a p=0.000	68.1	31.5 ^a p=0.000	36.8 ^a p=0.000	47.3			
Limbs	11.5 ^a p=0.032	21.0	9.3	26.3	14.8			
Arborising vessels	76.0 ^a p=0.000	42.0	77.8 ^a p=0.000	68.4	65.8	0.575	0.598	0.542
Short fine telangiectasia	36.1 ^{ab} p=0.000, p=0.012	72.3	44.4 ^a p=0.000	68.4	49.5	0.475	0.446	0.350
<20%	21.7	18.4	31.4	47.4 ^a p=0.012	23.0			
20–50%	10.1	28.6	5.5 ^a p=0.001	10.5	15.3			
>50%	4.3 ^a p=0.000	25.2	7.5 ^a p=0.012	10.5	11.3			
Shiny white to red areas	31.3 ^a p=0.000	62.2	40.7 ^a p=0.014	31.6 ^a p=0.024	41.8	0.523	0.622	0.556
Multiple blue-gray globules	42.3 ^a p=0.008	26.9	40.7	42.1	37.5	0.675	0.664	0.507
Multiple small erosions	22.6 ^a p=0.000	46.2	24.5 ^a p=0.011	36.8	30.5	0.341	0.526	0.290
Ovoid nests	41.8 ^a p=0.000	9.3	35.2 ^a p=0.000	10.5	29.8	0.681	0.624	0.610
Ulceration	31.7 ^a p=0.000	10.9	61.1 ^a p=0.000	36.8	29.8	0.735	0.781	0.684
Maple leaf	16.8	21.8	16.7	21.1	18.5	0.469	0.594	0.450
Spoke wheel	5.8	10.9	3.7	15.8	7.5	0.524	0.547	0.499
Concentric structures	5.3	8.4	7.4	15.8	7.0	0.239	0.335	0.113
Dots	54.3	43.7	46.3	52.6	50.0	0.6	0.715	0.598
Light brown nests	49.0 ^a p=0.001	30.3	26.3	42.1	40.5	0.776	0.609	0.524
Homogeneous nests	24.0 ^a p=0.000	8.4	13.0	21.1	17.8	0.658	0.447	0.523
Structured nests	37.0	26.9	14.3 ^c p=0.003	26.3	32.8	0.786	0.599	0.506

Significant with respect to ^asuperficial basal cell carcinomas (BCCs); ^bcombined BCCs; ^cnodular BCCs. κ 1 vs κ 2 represent the interobserver agreement between observer 1 and 2.

to histologic subtype. Arborising vessels were more frequently present in nodular, infiltrative and combined BCCs. On the contrary, short fine telangiectasia were more frequent and widespread in superficial BCCs.

Pigmented structures in the total BCC population, such as multiple blue-gray globules and large gray-blue ovoid nests, and ulceration were less frequently noticed in superficial BCCs, whereas in the latter, multiple small erosions prevailed. In 40.5% of BCCs some kind of

light brown nests were visible. Homogenous ones were appreciated in 17.8% of all BCCs, whereas structured nests were observed in 32.8%. Nests were more clearly visible at a 50–70-fold magnification (Fig. S1¹).

Table II illustrates the frequency of dermoscopic descriptors according to pigmentation extension. In

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1808>

Table II. Frequency of histologic subtype and dermoscopic features according to extension of pigmentation

	0% (n=84) %	<30% (n=111) %	30–70% (n=100) %	>70% (n=105) %
Nodular	38.1 ^a p=0.000	42.9 ^a p=0.000	48 ^a p=0.000	79.0
Superficial	46.4 ^a p=0.000	35.0 ^a p=0.000	29 ^a p=0.000	8.6
Infiltrative	14.3	14.3	15.0	10.5
Combined	1.2	8.9	8.0	0.9
Arborising vessels	70.2	67.6	59.0	66.7
Short fine telangiectasia	59.7 ^a p=0.000	61.3 ^a p=0.000	56.0 ^a p=0.000	21.9
<20%	20.3	24.3	31.0	16.2
20–50%	14.2	20.7	19.0	7.1
>50%	25.1 ^a p=0.000	16.2 ^a p=0.000	6.0	0.9
Shiny white to red areas	73.8 ^a p=0.000	49.3 ^a p=0.000	30.0 ^a p=0.029	16.2
Multiple blue-gray globules	1.2 ^a p=0.000	25.2 ^{ab} p=0.000	65.0 ^b p=0.000	58.6
Multiple small erosions	40.5 ^a p=0.009	34.2	27.0	21.9
Large blue-gray ovoid nests	0.0 ^a p=0.000	7.2 ^a p=0.000	36.0 ^a p=0.000	75.8
Ulceration	25.0	27.0	22.0 ^a p=0.000	45.0
Maple leaf-like areas	1.2 ^a p=0.000	18.0 ^b p=0.000	30.0 ^b p=0.000	24.9
Spoke wheel areas	0.0	7.2 ^b p=0.032	17.0 ^{ab} p=0.019, p=0.000	5.7
Concentric structures	1.2	7.2	14.0 ^b p=0.004	5.7
Dots	21.4 ^a p=0.000	49.5	64.0 ^b p=0.000	60.0
Light brown nests	14.3 ^a p=0.000	42.3 ^b p=0.000	54.0 ^b p=0.000	47.6
Homogeneous nests	7.1 ^a p=0.000	14.4 ^b p=0.000	22.0 ^b p=0.000	25.7
Structured nests	10.9 ^a p=0.000	36.0 ^b p=0.000	46.0 ^b p=0.000	34.3

Significant with respect to ^a> 70% pigmentation; ^b0% pigmentation.

non-pigmented lesions, superficial BCCs were prevalent, whereas in other pigmented categories nodular BCCs were more frequent. Arborising telangiectasia was consistently observed across all pigment subtypes, whereas short fine telangiectasia showed a decreasing trend according to pigmentation intensity, especially when widely distributed (>50%), along with shiny white to red areas and multiple small erosions. Pigmented structures such as large blue-gray ovoid nests, multiple blue-gray globules, maple leaf-like structures and spoke wheel areas were seldom noticed in non-pigmented BCCs. Light brown nests were visible in 14.3% of non-pigmented lesions, whereas in the other pigmentation groups these were observed in 42 to 54% of the cases.

Table S1¹ shows the frequency of dermoscopic features according to age, gender and skin location. No substantial differences were observed between subjects aged ≤ 60 years with respect to those over 60. In male subjects, arborising telangiectasia, ulceration and shiny white to red areas were more frequently seen than in women, whereas the latter more often presented short fine telangiectasia. In lesions localised on head/neck and trunk, arborising telangiectasia, multiple blue gray globules and maple leaf-like areas were more regularly observed, whereas on the limbs short fine telangiectasia and shiny white to red areas were more common than on head/neck. New descriptors were homogeneously distributed throughout all subgroups.

κ -values referring to inter-observed agreement are reported in Table I. The highest values refer to multiple blue-gray globules, ovoid nests and ulceration. κ -values for total light brown nests ranged between 0.776 and 0.524.

DISCUSSION

Dermoscopic features of BCC have been extensively studied and well defined (6–11, 15, 17–28), and their assessment has definitely improved the diagnosis of BCC (5). Dermoscopic descriptors are known to be strictly instrument dependent (15). In spite of this, that most studies of a large number of BCCs come from multicentre studies, that have not used uniform dermoscopic technology (or classification systems); and that, the dermoscopic appearance of BCCs is as varied as the histological appearance, and that correlations between dermoscopic and histological appearance have tended to rely on a limited number of cases. Finally, on reviewing the dermoscopic images referring to some BCCs, we felt that some aspects displayed by highly magnified images could be expressed only employing new descriptors. In this study, an evaluation of the frequency and reproducibility of already described BCC features was performed on a homogeneous image database, and new magnification-related descriptors were introduced.

The frequency reported in this study of the classic diagnostic markers of pigmented BCC, i.e. large blue-gray ovoid nests and multiple blue-gray globules, differs from that reported previously (7, 20). This may reflect the composition of the database, since, as shown here, these figures vary according to degree of pigmentation and histologic subtype: ovoid nests were found more frequently in nodular and pigmented BCCs with respect to superficial and non-pigmented ones.

In spite of the difficulty in distinguishing between large blue-gray ovoid nests, “i.e. well-circumscribed, confluent or near confluent pigmented ovoid or elongated areas, larger than globules and not intimately connected to pigmented tumour body”(6) from globules, which, in turn, “should be differentiated from multiple blue-gray dots”(6), reproducibility figures in this study were higher than those reported previously (10, 29).

We also found it challenging to identify “multiple in-focus blue-gray dots”(10), since most blue-gray dotted structures are blurred with unfocused boundaries. Thus, we decided to comprise all dotted structures in one parameter, i.e. dots, that were evaluated on the whole, irrespective of their colour. Employing this parameter, reproducibility figures were high.

Whereas pigmented structures are crucial for the diagnosis of pigmented BCC, vascular ones are employed for the diagnosis of BCC with scarce pigmentation. Arborising vessels are a prototypic feature of BCC associated with a high positive predictive value (6, 30, 31). A second, distinct vascular pattern is represented by short fine telangiectasia, consisting of short, small calibre vessels, interpreted as an early variant of arborising vessels. Both descriptors show satisfactory reproducibility figures, whereas their frequency varies according to histologic subtype, as also shown by the data presented in this paper: arborising vessels were more frequently observed in nodular and infiltrative BCCs, but an inverse frequency trend was observable for short fine telangiectasia, which were present in 70% of superficial BCCs.

Literature variations in the frequency of vascular patterns may also be due to the use of different instruments for image magnification and acquisition, such as employing polarised modalities or not. Liebman et al. (15) reported low levels of agreement between contact and non-contact dermoscopy for certain vascular features. This may be due to difficulties in recognising vascular patterns when performing contact dermoscopy, because of compression of blood vessels by the objective. Moreover, when observing BCC at a 10–20 fold magnification, vessels, and in particular, the tree-like distribution of vascular features may be difficult to recognise. Conversely, a 50–70 fold magnification enables the detection of tiny vascular branches with a tree-like or a hairpin distribution (Fig. S2¹). This may explain the higher frequencies of arborising vessels

and short fine telangiectasia reported in this study with respect to those of other reports.

The present incidence of superficial BCC is higher than previously noticed. At the Department of Dermatology of the University of Modena 5520 BCCs were removed during the years 2007–2011, and for 1,117 of these lesions the histologic diagnosis was superficial BCC. Besides nodular BCC, superficial BCC is one of the most common types typically occurring on the trunk as a scaly, pink to red-brown patch which can easily be ignored by the patient or doctors. Dermoscopy offers some help. In association with shiny white to red structure-less areas and multiple erosions, regarded as the initial stage of clear-cut ulceration, short fine telangiectasia has been proposed as a decisive diagnostic clue to superficial BCC diagnosis (7, 8, 32). These have to be differentiated from the homogenous vascular pattern associated to red dots on a light-red background typical of psoriasis, from dotted and linear vessels which can be detected in eczema and from a mixed vascular pattern in tinea (21).

According to literature data, erosions are found in 67–71% of superficial BCCs (7, 8). However, in our cases they were detected only in 46% of this type of lesion. Moreover, reproducibility was only moderate ($\kappa = 0.341$), probably because they are not always easily recognisable.

To the best of our knowledge, no sensitivity and specificity figures for superficial BCC versus inflammatory red patch skin diseases are available. Therefore, the introduction of a new descriptor not related to the vasculature, and potentially absent in inflammatory skin diseases, may be of great help for the diagnosis of superficial BCC.

Light brown nests were detected in 30.3% of superficial BCCs described in this study; light brown homogeneous nests were observed in 8.4% of these lesions, whereas structured nests including either gray-blue structures or aggregated dots or commas or both were found in 26.9%. Moreover, in BCCs totally lacking pigmentation, light brown nests were observed in 14.3% of the cases.

Light brown nests were more easily and frequently seen employing a 50–70 fold magnification, enabling the distinction of their faint boundaries on the light background. After a collegial evaluation of some significant images, each observer was able to easily identify this feature. In fact, reproducibility between the 2 more experienced observers was very good with κ -values ranging from 0.658 to 0.786. A weak point of this study consists in the fact that the authors knew that they were evaluating only BCCs, and this may potentially raise sensitivity scores of these new descriptors. Future studies involving control populations including other pigmented or non-pigmented lesions will specify their real frequency and the impact on the diagnosis of BCC.

In conclusion, the dermoscopic model proposed by Menzies et al. (6) to diagnose pigmented BCCs is not an effective discriminator for lesions lacking pigmentation. Based on our results, we hypothesise that brown dermoscopic nests described herein as an additional BCC criterion may avoid some diagnostic pitfalls and improve the early recognition of superficial BCCs and non-pigmented or slightly pigmented ones that may lack classic BCC patterns. For the detection of these structures high magnification dermoscopes are particularly effective.

The authors declare no conflict of interest.

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