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Dermoscopy of Nodular Melanoma: Review of the Literature and Report of 3 Cases

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ABSTRACT Nodular melanoma is the most aggressive subtype of melanoma, with rapid growth rate and metastatic potential. It is usually diagnosed at a locally advanced stage (Breslow thickness <2 mm) and is therefore associated with a poor prognosis. Nodular melanoma often does not fit the classic clinical ABCD criteria, but rather the EFG rule or 3 Cs criteria. Missing the diagnosis of nodular melanoma is a dermatologist's worst nightmare, especially since nodular melanomas can have a non-alarming clinical appearance and imitate a wide range of benign lesions. All evolving nodular lesions, despite their size, symmetry, and color, which cannot be confidently diagnosed as benign, should be excised in order to rule out nodular melanoma. Almost all melanoma-specific dermoscopic criteria are described in context of superficial spreading melanoma. Thus, physicians are not familiar and aware enough of dermoscopic features for early detection of nodular melanomas. Herein we present 3 cases of nodular melanomas from our Department and give a review of the current literature.

KEY WORDS: nodular melanoma; dermoscopic features; thin nodular melanoma

INTRODUCTION

The incidence of cutaneous melanoma (MM) has been increasing worldwide over the last decades. Since the melanoma prognosis is strongly associated with melanoma thickness, it is crucial to diagnose melanoma at the earliest stage possible in order to extend the patient's survival.

Nodular melanoma (NM) is the biologically most aggressive type of melanoma, with fast growth rate and metastatic potential, usually diagnosed at a locally advanced stage and associated with poor prognosis, which makes it a challenge for early recognition (1). The standard definition of NM relies on histopathological criteria: it is a melanoma growing vertically with only minimal horizontal spreading, not extending beyond the width of 3 rete ridges in any section (2,3). NM accounts for 15-30 % of all melanomas, which makes it the second most common type of melanoma after superficial spreading melanoma (SSM). It also constitutes for 40-50 % of melanomas thicker than 2 mm, making NM the leading cause of melanoma deaths (4). A group of authors found that the median Breslow thickness of NM at the time of diagnosis was significantly greater than that of the non-nodular invasive melanoma (2.7 mm vs. 0.7 mm) (3). Incidence, thickness at the time of diagnosis, and mortality rates of NM have been constant in the last 15-20 years despite advances in diagnostic algorithms and medical technology (1). The incidence of NM increases with age; it is usually found in men older than 50 years with sun damaged skin. NM is most

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frequently located in the head and neck area or the lower limbs (5).

In this article, we present a review of the current literature concerning the main characteristics of nodular melanoma, with particular emphasis on dermoscopic features. We also present 3 cases of nodular melanoma from our Department which are discussed in the context of the review of this particular type of melanoma.

MAIN CHARACTERISTICS OF NODULAR MELANOMA AND DIFFERENCES FROM SUPERFICIAL SPREADING MELANOMA

Risk factors

NM is associated with smaller total number of nevi compared to SSM (5), which points to the fact that patients with NM frequently lack the prototypic phenotypic appearance of a patient at high risk for melanoma (6). It has been found that NM correlates with actinic keratoses and epidermal carcinomas (both baseocellular and squamous cell types) which suggests stronger correlation of NM with severely sun damaged skin than high nevi counts (1).

Clinical findings

NM is usually represented as a symmetric or asymmetric, regularly bordered, elevated, firm, evenly colored, hypomelanotic or amelanotic papule or nodule, which grows rapidly and can eventually bleed or ulcerate (7). The colors found in NM vary from black, grey, blue, brown, and pink, including different shades of one of these colors or their combination. The surface of NM can be smooth, rough, or scaly. Since melanocytes regulate differentiation and proliferation of keratinocytes, scale is a result of increased keratinocytes turnover (8). What makes NM sometimes difficult to diagnose is the fact that it usually lacks the classic ABCD criteria (asymmetry, border irregularity, color variation, and diameter >6 mm) seen in SSM and other melanoma subtypes. For this reason, two additional clinical criteria, i.e. 3 Cs criteria and the EFG rule, are also used. The EFG rule is an acronym that summarizes the most frequent clinical features of NM, which are elevation, being firm to palpation, and continuous growth for 1 month (9). 3 Cs criteria is an acronym denoting color, contour, and change. Addition of the 3Cs criteria and EFG rule to the classic ABCD criteria helps in detection of lesions that might be missed when using ABCD criteria alone (6). Menzies *et al*. found that NM occurred more frequently as amelanotic/hypomelanotic (37.3%) than invasive non-NM (7.5%) (3). In 5.8% of NM-a cases, a symmetrical pigment pattern is found, more frequently in pigmented nodular *vs*. non-nodular invasive melanoma (0.8%), which is an important cause for misdiagnosis using standard dermoscopic criteria (3).

Differential diagnosis

The differential diagnosis of NM is often challenging and includes a wide spectrum of both benign and malignant, melanocytic and non-melanocytic, inflammatory, and infective lesions. However, the most common differential diagnoses are: basocellular carcinoma (BCC), squamous cell carcinoma (SCC), hemangioma/angiokeratoma, pyogenic granuloma, Kaposi sarcoma, dermatofibroma, seborrheic keratosis, other types of MM (amelanotic/hypomelanotic melanoma and desmoplastic melanoma), nevi (congenital, combined, Spitz, and blue nevi), and MM metastasis (10).

Histopathological findings

In most cases, rapid downward growth of NM is seen in the shape of huge dermal nests and sheets of cytologically atypical melanocytes of various histological morphology (spindle shape cells, epithelioid cells, balloon cell change) (11). In contrast to SSM, which histopathologically shows characteristically prominent pagetoid spreading, NM presents vertical growth with a radial growth phase not extending the width of 3 rete ridges beyond the invasive component in any section (12).

Dermoscopic differences from SSM and other melanoma subtypes

Since NM shows fast downward (invasive) growth, it does not usually show color change, a multicomponent pattern, or dermoscopic features associated with radial growth phase melanomas or thin melanomas (pseudopods, atypical or inverse network, branched streaks) (13). In the majority of NMs, epidermal and dermal changes are sparse and only few colors and structures are seen.

DERMOSCOPY OF NODULAR MELANOMA

NM presents with these dermoscopic features more frequently compared with non-NM:

1) Symmetrical or asymmetrical shape; nearly 6% of NM shows symmetry in all axes;

2) Symmetrical pigmentation pattern; when a progressively growing, symmetrically patterned melanocytic nodule is identified, NM needs to be excluded (3);

3) Black color; due to melanin located in atypical melanocytes within the upper layers of epidermis; it can usually be found in irregularly sized, shaped, and unevenly distributed dots and globules or large irregular blotches;

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4) Black dots and globules are an important diagnostic sign of pigmented NM, especially when found peripherally; they are commonly irregular in size and shape and irregularly distributed throughout the lesion;

5) Areas of homogenous blue pigmentation; presence of melanin (in melanocytes or in melanophages) in the dermis gives the blue color in dermoscopy. Since NM usually presents with rapid vertical growth, blue color can be seen in these cases;

6) Blue-black rule; a new feature first described by Argenziano *et al*. (10), representing a useful tool in the diagnosis of pigmented NM. Blue-black (BB) color or the blue-black rule is defined as the presence of a combination of blue and black pigmented areas involving at least 10% of the lesion surface. The presence of these two colors means that the pigment is present in mid-deep dermis (blue color) and in atypical melanocytes within the epidermis (black color). However, the blue-black rule is considered absent in cases in which the black color is located in recognizable comedo-like openings (typical for seborrheic keratoses) or lacunae (typical for hemangiomas). The importance of the BB rule lies in the fact that the combined method based on the presence of either the BB feature or one (or more) of the standard melanoma-specific criteria reaches 84.6% sensitivity, with 80.5% specificity and 93.2% negative predictive value for MM recognition (10);

7) Blue-white veil; irregular, structureless areas of confluent blue pigmentation with an overlying white "ground-glass" film usually associated with invasive melanomas (14). Histopathologically, in NM it correlates with heavily pigmented nests of melanocytes or melanophages in the dermis with various amounts of fibrosis (15);

8) Polarizing specific white lines, also named "crystalline/chrysalis structures", can only be seen with a polarizing dermatoscope as white shiny short lines; histopathologically they correlate with vertical bands of collagen-reflecting increased fibroblast activity related to the vertical growth phase of melanoma (16). White lines can also be found in dermatofibroma (DF) and basocellular carcinoma (BCC), but in MM they are short and orthogonally distributed;

9) Structureless/featureless areas (3); a homogenous area of varying colors, without a particular pattern or features seen in melanocytic or non-melanocytic lesions, it is commonly found in invasive and thick lesions due to the fact that with vertical progression of the tumor less and less dermoscopic features are seen;

10) Pink color; (especially different shades of pink) is seen in amelanotic or hypomelanotic nodular melanoma. It is due to lack of melanin (regression, amelanotic melanoma) and neovascularization;

11) Milky red/pink areas; refers to milky red globules or a pinkish background area indicating greater angiogenesis, usually not seen in benign lesions, but it is an important feature of amelanotic/hypomelanotic NM. A combination of dotted and linear irregular vessels over a milky red background with/without chrysalis-like structures or reticular depigmentation is also highly suggestive of invasive MM (17);

12) Atypical vascular pattern, including polymorphous blood vessels (defined as the presence of more than one morphological type of vessels) in irregular distribution. It is important to note that the vascular pattern and vessel arrangement strongly depends on the tumor thickness. Regularly arranged homogenous dotted vessels are found predominantly in (early) flat tumors, in contrast to the thick or raised tumors witch show irregularly distributed longer and coarser vessels of varying shape (17). The most common vascular pattern seen in NM (especially of hypomelanotic and amelanotic type) is the combination of dotted, hairpin, and linear irregular vessels in uneven distribution;

13) Predominant peripheral and large diameter vessels which are twice more frequently found in thick melanomas (>1 mm Breslow thickness) then thin melanomas (<0.75 mm) (18).

DERMOSCOPY OF THIN NODULAR MELANOMA

There are only very limited data on dermoscopy of thin nodular melanoma. These patients do not fit into the category of high-risk patients and are not usually seen by a dermatologist on a regular basis. As already noted, most nodular melanomas are first detected by patients, their family, or general practitioners.

Kalhoran *et al*. (6) studied 11 thin nodular melanomas (Breslow thickness <1.3 mm) and found that they show a subtle clinical appearance but have dermoscopic clues to malignancy. These selected dermoscopic elements are: homogeneous disorganized pattern, asymmetry, blue-white veil, structureless areas, and atypical vascular structures (6). Because these dermoscopic characteristics of thin NM-s appear more suggestive of malignancy than do the clinical features, dermoscopic analysis of clinically new or changing lesions may aid in their earlier detection (6).

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CASE REPORTS

Case 1

A female patient, 74 years of age, was referred to our Department due to a black lesion with continuous growth located on her scalp. The patient noticed the lesion 3 months before she came to our Department (Table 1; Figure 1, a). She was advised by her general practitioner to use heparin-sodium ointment with no result. Dermoscopy showed: asymmetry of outline, color, and structures, a blue-white veil, a large blue-grey structureless area, a structureless brown area at 5-7 o'clock, and crusting on the surface (Table 2; Figure 1, b). We performed an urgent excision. Histopathology confirmed diagnosis of nodular melanoma (pT3aNx9), Breslow thickness 2.3 mm.

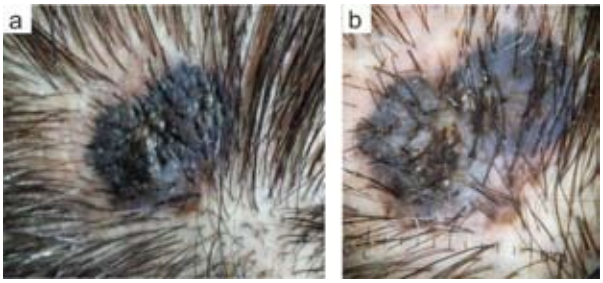

Figure 1. (a) Black nodular lesion located on the scalp. (b) Dermoscopy: asymmetry of outline, color, and structures, blue-white veil, large blue-grey structureless area, structureless brown area at 5-7 o'clock and crusting on the surface.

Case 2

A female patient, 57 years of age, with history of multiple sunburns, a month ago noticed growth of previously small nodular lesion located on the right scapular area and development of a small red nodule at one edge of the lesion (Table 1; Figure 2, a). Dermoscopy showed a sharply circumscribed lesion with different shades of brown and red color, a blue-white veil, white shinny lines, scaling on the surface, and a small bright red nodular lesion at 3 o'clock on one edge (Table 2; Figure 2, b). Our differential diagnosis was: nodular melanoma, collision lesion (nodular melanoma and hemangioma, less likely granuloma pyogenicum). Complete excision was performed, and histopathology revealed nodular melanoma (pT4b), Breslow thickness 7.1 mm.

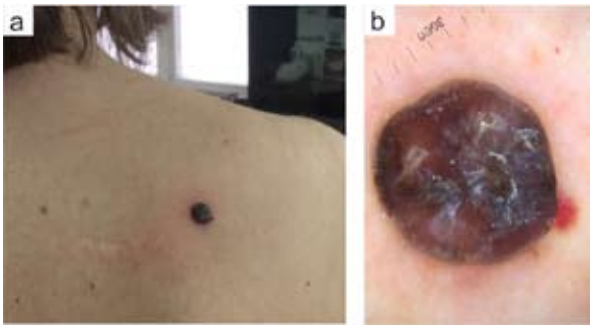

Figure 2. (a) Dark-brown nodule located on the back. (b) Dermoscopy: sharply circumscribed lesion, with different shades of brown and red color, blue-white veil, white shinny lines, scaling on the surface, and a small bright red nodular lesion at 3 o'clock on one edge.

Case 3

A female patient, 52 years of age, noticed progressive growth of a heavily pigmented nodular lesion with a slightly keratotic surface, 9×6 mm in size, located on the right arm (Table 1; Figure 3, a). Dermoscopy showed asymmetry of colors and structures, multiple colors (brown, black, and grey), a blue-white veil, irregularly sized and shaped globules unevenly distributed throughout the lesion, and scaling on the surface (Table 2; Figure 3, b). Our differential diagnosis was: nodular melanoma and Spitzoid melanoma. Excisional biopsy was performed, and histopathology revealed nodular melanoma, Breslow thickness 1.66 mm.

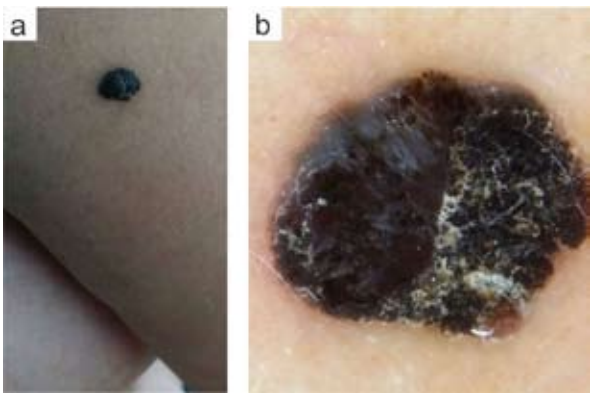

Figure 3. (a) Darkly pigmented nodular lesion with slightly keratotic surface located on the arm. (b) Dermoscopy: asymmetry of colors and structures, multiple colors (brown, black, and grey), blue-white veil, irregularly sized and shaped globules unevenly distributed throughout the lesion, and scaling on the surface.

Table 1. Patient and lesion details of 3 nodular melanoma cases

Case	Sex	Age	Self-discovery	Previous skin cancers	Lesion location	**Scaling**	**Breslow thickness (mm)**
1	Female	74	yes	no	scalp	yes	2.3
2	Female	57	yes	no	back	yes	7.1
3	Female	52	yes	no	arm	yes	1.66

COMMENT/DISCUSSION

Most of dermoscopic criteria for melanoma are for SSM as well as LMM (lentigo maligna melanoma), and ALM (acrolentiginous melanoma). Nodular melanoma is the most aggressive type with a very poor prognosis, accounting for the majority deaths from melanoma. However, the combination of clinical ABCD criteria, 3 Cs criteria, and the EFG rule as well as dermoscopic melanoma-specific criteria with the BB rule can be helpful. Furthermore, education of patients and general practitioners can help facilitate and shorten the procedure of getting to a specialist. Since this type of melanoma grows rapidly, early suspicion of the diagnosis and early detections are essential.

The cases of NM from our Department were all found in women over 50 years of age with no history of previous skin cancer. The lesions were all first noticed by the patients themselves, since they were all heavily pigmented and rapidly growing nodular lesions with a slightly scaly surface (Table 1). In all 3 cases, histopathology confirmed the final diagnosis of thick NM. In all of these 3 cases (Table 2), dermoscopy showed structureless/featureless areas, and in one case a blue-white veil, which are hallmarks of thick invasive lesions. A symmetrical shape and pigmentation pattern, black and blue color, the BB-rule, black dots/globules, and crystalline structures were also commonly found (33.3%). The absence of pink color and milky red areas was expected, since none of the cases were amelanotic/hypomelanotic melanomas, but in the case of very thick NM (case 2 – Breslow thickness 7.1 mm) one would expect to find peripherally located large-diameter, vessels which were absent.

CONCLUSION

NM is the most aggressive subtype of melanoma with distinct histopathological characteristics and biological behavior, compared with SSM. NM has a faster growth rate (GR) (median GR 0.49 mm/month) (19) compared with other melanoma subtypes, e.g., lentigo maligna melanoma (median GR 0.13 mm/month) and superficial spreading melanoma (median GR 0.12 mm/month) (1). Frequently, it is the rapid growth of the lesion that draws the attention of the patients themselves, a family member, or the general practitioner (13). NM is usually discovered by the patient (60.6 %) (7), or by another family member and the patient (17%) (20). Given the fact that NM is usually discovered by the patients themselves and due to the high growth rate which allows it to arise between two regular skin examination appointments, it is crucial to educate patients on how to perform a proper self-examination of the skin and enable rapid access to dermatologists when a suspicious lesion is noticed (6).

Dermoscopy increases detection of early NMs, with dermoscopic features typically more suggestive

Table 2. Dermoscopy features of 3 nodular melanoma cases

Dermoscopic features	**Case 1**	**Case 2**	**Case 3**
Symmetrical shape	no	yes	no
Symmetrical pigmentation pattern	no	yes	no
Black color	no	no	yes
Black dots	no	no	yes
Areas of homogenous blue pigmentation	yes	no	no
Blue-black rule	no	no	yes
Blue-white veil	yes	yes	yes
Crystalline/chrysalis structures	no	yes	no
Structureless/featureless areas	yes	yes	yes
Pink color	no	no	no
Milky red/pink areas	no	no	no
Atypical vascular pattern	no	yes	no
Predominant large diameter and peripheral vessels	no	no	no

of malignancy than clinical ones; it should be regularly used by physicians as a part of skin examination to analyze suspicious lesions. NM, especially if hypomelanotic, can easily be mistaken for benign lesions or non-melanoma skin tumors. Therefore, papular or nodular lesions, symmetric or asymmetric, pigmented or non-pigmented, firm to palpation, rapidly growing for more than a 1-month period, especially if recently developed at a mature age and if there is any indication of malignancy, should not be simply monitored, but rather excised in order to exclude NM (1,21).

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