Dermatology Practical & Conceptual

Identification of Novel Dermoscopic Patterns for "Featureless Melanoma": Clinical-Pathological Correlation

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ABSTRACT

Introduction: Diagnosis of melanoma can be very difficult because of its phenotypic and histological heterogeneity. Difficult-to-diagnose melanoma can be represented by mucosal melanoma, pink lesions, amelanotic melanoma (amelanotic lentigo maligna, amelanotic acral melanoma, desmoplastic melanoma), melanoma arising on sun-damaged facial skin, and "featureless melanoma".

Objectives: The aim of the study was to improve the identification of featureless melanoma (scoring 0-2 according to the 7-point-checklist) describing the variegated dermoscopic features and their histopathological correlation.

Methods: Study samples included all melanomas excised based on clinical and/or dermoscopic findings in the period between January 2017 and April 2021. Before excisional biopsy, all lesions were recorded by means of digital dermoscopy at the department of Dermatology. Only lesions with a diagnosis of melanoma and a high quality of dermoscopic images were included in this study. After clinical and dermoscopic evaluation of 7-point checklist score, single dermoscopic and histological features were considered for lesions with a score of 2 or lower and a diagnosis of melanoma (corresponding to dermoscopic featureless melanoma).

Results: A total of 691 melanomas fulfilled inclusion criteria and were retrieved from the database. The 7-point checklist evaluation identified 19 "negative-featureless" melanoma. The 100% of the lesions with score 1 showed a globular pattern.

Conclusions: Dermoscopy is still the best diagnostic method for melanoma. The 7-point checklist provides a simplification of standard pattern analysis because of the algorithm based on a scoring system and the lower number of features to recognize. In the daily practice it is more comfortable for many clinicians to keep in mind a list of principles that may help in the decision.

Introduction

Melanoma

Melanoma is one of the most aggressive forms of malignant skin cancer deriving from altered and atypical neural crest-derived melanocytes principally localized in the hair follicles and in the basal layer of the epidermidis, and along the meninges, choroid, and mucosal surfaces too. It accounts about 3% of the overall skin cancers diagnosed each year and can develop from benign nevomelanocytic lesions, or, more frequently, from normal-appearing skin, as result of a complex interplay of genetic, environmental, and constitutional elements [1-3]. The worldwide incidence of cutaneous melanoma has been growing annually with a very rapid rate placing itself as the 15th most common tumor globally [2].

The most important predictive prognostic factor is the type of growth. The radial growth phase (RGP), typical of melanoma in situ, defines a disease which is still localized and restricted to the epidermidis, above the dermal-epidermal junction showing a pagetoid spread within the skin. The vertical growth phase (VGP), further classified into an early and a late stage, is characterized by the presence of dermal tumoral nests, extending, sometimes, into subcutaneous fat.

Difficult Melanomas

One of the hardest challenges is the amelanotic melanoma occurring in about 2% of all malignant melanomas. It is more frequent in red hair patients with skin type I, freckles, a sun-sensitive phenotype, a previous history of amelanotic melanoma or lack of naevi on the back [4,5]. In 1999 Koch et al defined the amelanotic melanoma as "the great masquerader" referring to the lack of the clinical hallmark of cutaneous melanoma, that is the presence of several amounts of melanic pigment within the tumor, determining misdiagnoses [6]. Amelanotic melanoma may be confused with different benign (intradermal naevus, seborrheic keratosis, eczema, actinic keratosis, granuloma annulare, pyogenic granuloma, verruca vulgaris, naevus depigmentosus, scar, dermatofibroma, lymphocytoma cutis) and malignant (basal cell carcinoma, Merkel cell carcinoma, Bowen disease, keratoacanthoma, atypical fibroxanthoma, extramammary Paget disease, malignant fibrous histiocytoma, malignant schwannoma, squamous cell carcinoma) clinical conditions [5,6]. The most stringent authors define a melanoma truly amelanotic when there is a clinically and dermoscopically lack of pigmentation with melanin in less than 5% of tumor cells on histological examination [5].

Any clinical subtypes of cutaneous melanoma may be amelanotic, considering the desmoplastic melanoma as the most frequent type and the subungual site the most common localization. Desmoplastic melanoma is a rare subtype with a nodular or a scar-like appearance. A primarily dermal component of spindle cells represents the main histological finding. Most frequent in Caucasian people aged sixty to seventy years and in sun-exposed areas of head and neck region. Desmoplastic melanoma is more likely a sarcoma, considering the local aggressive biological behavior and the predisposition for local and visceral growth [3].

Pink lesions often represent a challenging diagnosis for the absence of the identifiable peculiar characteristics using conventional methods, for example, epiluminescence microscopy. They constitute a very wide and heterogeneous group of skin lesions of inflammatory and/or benign/malignant neoplastic origin [7]. Dermoscopy is still far from an accurate diagnosis about pink lesions, considering a rapid identification crucial in the case of amelanotic melanoma or, even worse, nodular amelanotic malignant melanoma. In these cases, particular dermoscopy findings include an irregular shaped vascularization (linear, dotted, or globular vessels having an irregular distribution), whitish/depigmented areas, and ulceration [7].

Primary mucosal melanoma was first described in 1856 by Weber et al [8]. Nowadays, despite its rarity, mucosal melanoma is of great interest because of its worse prognosis compared to cutaneous subtype. Overall, only 0.8%-3.7% are mucosal melanomas and, contrary to the recent growing incidence of cutaneous melanoma, its incidence tends to stay stable [9]. No association to any viral infections (human herpes viruses, human papilloma viruses, and polyomavirus), ultraviolet (UV) radiation exposure or racial differences. Its etio-pathogenesis remains unclear. Contrary to cutaneous melanoma, C-KIT is overexpressed in about 80% of mucosal melanomas [9]. Mucosal melanoma can be localized within the mucosal membranes of the gastrointestinal, respiratory, and genitourinary tract. Head and neck are the most common anatomic sites, in which the prognosis is believed to be better [9].

Facial pigmented lesions are often equivocal for the particular skin anatomic architecture of the face as a result of

the absence of the rete ridges, the importance of adnexal structures and the varying degrees of sun-damaged epidermidis and solar elastosis in the dermis [10]. They commonly show a pseudo-network pattern bordering the unpigmented hair follicle openings [10].

Acral lentiginous melanoma is another type of melanoma whose diagnosis is still challenging. Its predilection for acral sites determinates a delayed diagnosis at later stages associated to a worse prognosis. An association between mechanical stress and acral melanoma has been proposed, but further investigations are necessary about it [11].

Featureless Melanoma

ABCDE rule (Asymmetry, Border, Color, Diameter, Evolving) only provides 64% accuracy, indicating a necessity to have alternative diagnostic tools. The 7-point checklist score provides a useful algorithm for dermoscopy.

In 1998 Argenziano et al introduced a new ELM 7-point checklist [12]. They identified seven standard ELM criteria, selected by their prevalence in melanoma cases and their histopathological correlates. According to odds ratios calculated, a score of 2 was given to 3 criteria (odd ratio more than 5) defined as "major" criteria, and a score of 1 was allowed to the remaining 4 criteria (odd ratio lower than 5) called "minor" criteria. A minimum total score of 3 was necessary for diagnosis of melanoma [12,13].

This new diagnostic algorithm revealed a sensitivity of 97% (percentage of dermoscopic images of melanoma scored as melanomas), a specificity of 71% (percentage of dermoscopic images of naevi scored as benign naevi) with a diagnostic accuracy for melanoma of 68%, greater parameters compared to the ABCDE rule [12].

To increase sensitivity, a 7-point checklist revisited with a lower threshold for surgical excision has been proposed in 2011 by Argenziano et al [14]. One point was attributed to each dermoscopic feature (without differentiation between major criteria and minor ones) and the presence of only one finding was sufficient to propose removal. The necessity to introduce an additional diagnostic tool arises from new knowledges about dermoscopy [14].

Objectives

The aim of the study was to improve the identification of featureless melanoma (scoring 0-2 according to the 7-point-checklist) describing the variegated dermoscopic features and their histopathological correlation.

Methods

Study samples included all melanomas excised based on clinical and/or dermoscopic findings in the period between January 2017 and April 2021. Before excisional biopsy, all lesions were recorded by means of digital dermoscopy at the department of Dermatology, University of Modena and Reggio Emilia. Only lesions with a diagnosis of melanoma and a high quality of dermoscopic images were included in this study. After clinical and dermoscopic evaluation of 7-point checklist score, single dermoscopic and histological features were considered for lesions with a score of 2 or lower and a diagnosis of melanoma (corresponding to dermoscopic featureless melanoma).

The study was conducted according to the criteria set by the declaration of Helsinki.

Instruments

For each lesion a complete set of clinical and dermoscopic images, including the whole lesion, along with histopathology were available. Dermoscopic images were carried out by means of Dermlite Photo (3GEN®) equipped with a Canon G12 Camera.

Dermoscopic Criteria

The 7-point checklist score was calculated for each lesion as well as the frequencies of each different dermoscopic finding accounting for the score. Subsequently, melanomas with a total score of 2 or lower, according the 7-point checklist score, were classified as "featureless melanoma".

Histopathological Analysis

The histopathological analysis was performed by a Board-Certified Pathologist (AMC).

Statistics

Frequencies for each dermoscopic parameters were calculated in melanomas for each 7-point checklist score.

Results

A total of 691 melanomas fulfilled inclusion criteria and were retrieved from the database. The 7-point checklist evaluation identified 19 "negative-featureless" melanomas scored between 0 and 2, 194 lesions scored between 3 and 4 and 478 lesions scored between 5 and 10 (Table 1).

In the population with score ranging from 0 to 2, 8t melanomas were not showing any positive dermoscopic clue (Figure 1 and 2), 3 presented a score 1, and 8 with total score 2 (6 presented one major feature positive and 2 having a positivity in two minor ones).

Concerning the subgroup with a score of 3-4, 25 were associated with score 3 (23 presented 1 major feature with a minor one, and in only 2 cases we found a positivity in 3 minor criteria), while 169 had a score of 4.

Frequencies of the dermoscopic features in lesions with the 7-point checklist ranging 0-2 and score 3 are reported in Table 2 and Table 3, respectively.

In the population with a score of 1, the only positive criterion was irregular dots and globules (100%). Concerning the population scoring 2, the most frequent feature was the atypical network (75%), followed by irregular dots and globules (25%).

Concerning the population with 7-point checklist score 3, the most representative features were irregular dots and globules (84%) and atypical network (72%), followed by irregular diffuse pigmentation (16%), regression pattern (12%) and blue-whitish veil (12%).

In this work we present 19 difficult-to-diagnose-melanomas in which the only dermoscopic evaluation could not play a diagnostic role. Invaluable aids to improve sensibility and specificity for melanoma are represented by anamnesis, the ugly duckling sign, the signature naevus concept and clinical-dermoscopic follow-up. In this context, the aim of this study was to identify the most frequent dermoscopic and histopathological features of "featureless melanoma" trying to establish additional findings, too. All tumors, except for a case with score 0 (superficial spreading melanoma with a 0.34 mm Breslow thickness), were in situ melanomas.

In the population scoring 1, the 100% of the lesions showed a globular pattern. In a published previous work, as in our study, this pattern was found to be the rarest dermoscopic subtype of in situ melanoma (0.04% in the current case series versus 2.6% in the previous one) and never arising on a naevus [15].

Table 1. Distribution of the study population according to the 7-point checklist score.

7-Point checklist score	MM	% of MM
0	8	1.2%
1	3	0.04%
2	8	1.2%
3	25	3.8%
4	169	24.3%
5	119	17.2%
6	193	28%
7	76	11%
8	39	5.6%
9	33	4.8%
10	18	2.6%
TOT	691	100%

MM = malignant melanoma.

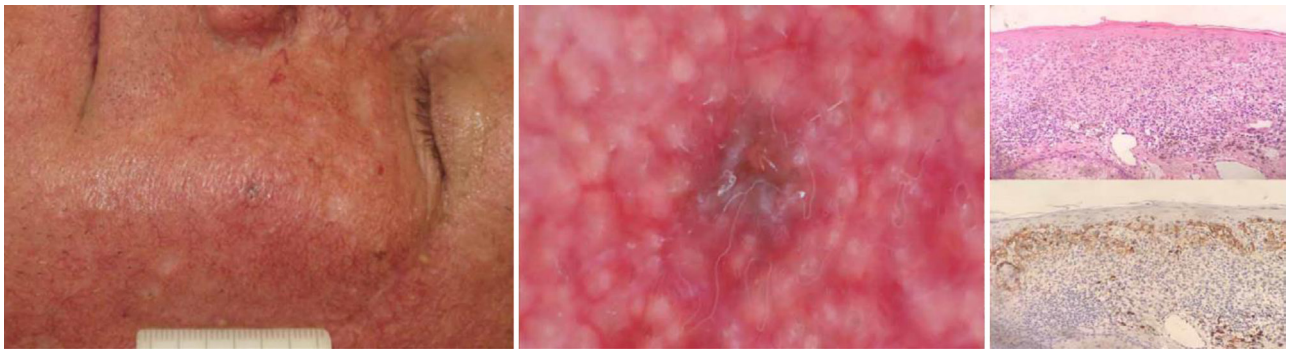

Figure 1. Facial featureless melanoma scoring 0 of a patient sun-damaged skin affecting by rosacea. Any melanoma findings are recognizable by dermoscopy. The HMB-45 staining, in the lower part of the right side, identify dermal and hypodermal tumoral nests.

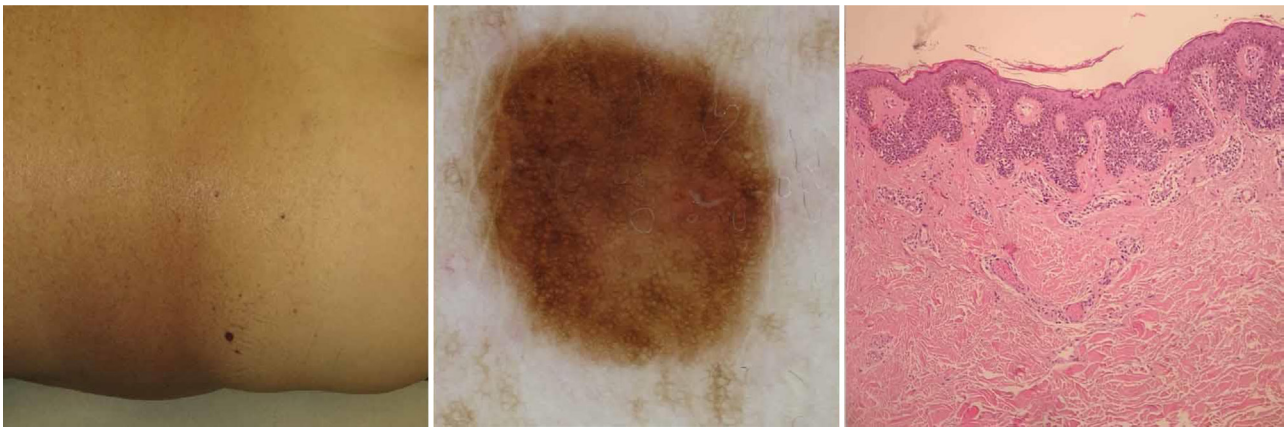

Figure 2. Featureless melanoma with score of 0 showing a regular pigmented pattern. In the right side of the picture, it is possible to see the histopathological image with irregular melanocytic nests along the rete ridges.

Table 2. Frequencies of dermoscopic features in lesions with 7-point checklist score 0-2.

Dermoscopic features	Score 0	Score 1	Score 2
Atypical network	-	-	6 (75%)
Blue-whitish veil	-	-	-
Atypical vessels	-	-	-
Irregular diffuse pigmentation (blotches)	-	-	1 (12.5%)
Peripheral streaks and/or pseudopods	-	-	-
Irregular dots and globules	-	3 (100%)	2 (25%)
Regression pattern	-	-	1 (12.5%)
TOT	8	3	8

Table 3. Frequencies of dermoscopic features in lesions with 7-point checklist score 3.

Dermoscopic features	Score 3
Atypical network	18 (72%)
Blue-whitish veil	3 (12%)
Atypical vessels	2 (8%)
Irregular diffuse pigmentation (blotches)	4 (16%)
Peripheral streaks and/or pseudopods	1 (4%)
Irregular dots and globules	21 (84%)
Regression pattern	3 (12%)
TOT	25

About melanomas with score 2, three-quarters of the cases presented a reticular pattern, in the remaining two lesions we noticed a globular patterns with additional regression areas and irregular blotches, respectively. This last was an in situ melanoma arising on a compound nevocytic naevus, showing, as additional feature, an inverse network. Prominent skin marks (linear hypopigmented furrows with an intersecting pattern) were found in other two cases. According to several authors, the last dermoscopic finding is a helpful indicator to differentiate an early or an in situ melanoma, especially on sun-damages skin, from a benign naevus [16]. Supplementary features were considered. In one lesion we noticed angulated lines (gray-brown not intersecting lines that meet at angles larger than 90 degrees and can form polygonal shapes, rhomboids and zigzag pattern [17].

In the subgroup with 0 points, one lesion, not presenting neither classic nor additional features, was arose on a benign melanocytic naevus. Two melanomas showed as unique finding the inverse network, one of which having the prominence skin marks, too.

Borderline positive melanomas scoring 3 manifested mostly irregular dots and globules, followed by atypical network. Supplementary features were considered. In two of twenty-five lesions the prominent skin marks were noticed, angulated lines in one case, and another one presenting both findings. In this group we have a case of melanoma, arisen on a compound benign naevus and with a Breslow thickness 0.3mm, exhibiting, as peculiar dermoscopic characteristic, crystalline or chrysalis structures. The presence of these findings is highly indicative of invasive melanoma (ticker than those without them) and cutaneous melanoma metastases [18].

Conclusions

Despite most research about dermoscopy has been managed in white skinned populations and few evidence about an equal ability to work well in non-white populations, dermoscopy is still the best diagnostic method for melanoma.

The 7-point checklist provides a simplification of standard pattern analysis because of the algorithm based on a scoring system and the lower number of features to recognize. Compared with the latter, the specificity of the 7-point checklist method is worse (75% versus 90%) for its propensity to overclassify atypical melanocytic lesions as melanoma. On the other hand, its sensibility is greater (95%), particularly for the early forms of cutaneous melanomas. This algorithm can be learned more easily by nonexpert dermatologists.

In the daily practice it is more comfortable for many clinicians to keep in mind a list of principles that trigger excision. In 2012, Lallas et al, edited several management rules to recognize some difficult melanomas using an integrating approach between clinical, dermoscopic, and histological examinations [21]). They summarized in seven simple and practical rules: 1) Look basically at all lesions, 2) Undress high-risk patients (patients with a personal or family history of melanoma or other skin cancers, people under 50 years presenting more than twenty naevi on the arms, patients over the age of 50 years with a chronic solar damage), 3) Use the "10 second rule" in single lesions (an approximated period to reach a conclusion in doubtful lesions), 4) Compare and monitor multiple moles (considering that each patient has a naevi's individual phenotype, this principle results very useful in cases of atypical mole syndrome where the previous rule could be ineffective), 5) Excise doubtful nodular lesions (especially for nodules positive to blue-black rule, milky-red areas and/or polymorphous vascular pattern), 6) Combine clinical and dermoscopic criteria, 7) Combine clinical and

histopathological criteria (for example, in cases of spitzoid tumors, or, similarly, in cases of naevus-associated melanoma or lesions showing a high degree of regression) [19].

In our experience, additional four rules can be memorize with the previous seven, that is: 8) Biopsy lesions with unspecific pigment pattern (desmoplastic melanoma can be the classic example), 9) Biopsy lesions with spitzoid features (especially in adults), 10) Biopsy lesions with extensive regression features (it has been demonstrated that in a contest of no melanoma-specific criteria, the probability for a lesion being melanoma growths consistently with the extent of regression seen with dermoscopy), 11) Biopsy pink lesions with an atypical vascular pattern [20].

Reduction in thickness increases the complexity of melanoma diagnosis. Several dermoscopy subgroups of in situ melanoma have been described, assuming a different origin or biological behavior of the tumor [15,20].

Further study will be needed to increase sensibility.

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