Dermoscopic features predicting the presence of mitoses in thin melanoma

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**ARTICLE INFO**

Article history:
Received 16 December 2016
Received in revised form 20 January 2017
Accepted 30 January 2017

Keyword:
Dermoscopy
Mitosis
Melanoma

**ABSTRACT**

Background: The latest AJCC classification has included the number of mitoses as a factor for upstaging thin melanomas. Meanwhile, dermoscopy has often been used to predict melanoma thickness, its value in predicting number of mitoses remains unknown.

Objective: Our aim is to evaluate the correlation between dermoscopic features and the presence of mitoses in a consecutive cohort of thin melanomas.

Methods: A case control study has been performed to identify specific dermoscopic parameters that could differentiate thin melanomas with 1 or more mitoses per mm² from those without mitoses.

Results: Of 177 melanomas equal to or thinner than 1 mm, 131 (74%) lesions had no mitoses and 46 (36%) lesions had at least 1 mitosis × mm². Dermoscopic features associated with the presence of 1 or more mitoses were the following: peripheral streaks (OR 4.11; 95% CI 1.94–8.71) and black colour (OR 4.70; 95% CI 2.28–9.68). In contrast, atypical pigment network (OR 0.30; 95% CI 0.15–0.61) and brown colour (OR 0.36; 95% CI 0.18–0.75) were associated to melanomas without mitoses. The same variables were also associated to the increasing number of mitoses at linear regression.

Conclusion: Black colour and peripheral streaks can predict the presence of mitoses in thin melanoma, while atypical pigment network and brown colour are associated to thin melanoma without mitoses.

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1. Introduction

Dermoscopy is a pivotal imaging tool that is currently regarded as gold standard for the preoperative diagnosis of melanoma [1]. In addition, dermoscopy provides a relatively good preoperative assessment of melanoma thickness [2,3]. More specifically, the presence of an irregular pigment network has been significantly associated to thin melanomas (with a Breslow thickness of less than 0.75 mm), while the present of blue-white veil and atypical vascular patterns have been associated to thicker melanomas (Breslow > 0.75 mm) [2]. Another study assessing the value of dermoscopy to predict sentinel lymph node (SLN) positivity [3] demonstrated that the presence of ulceration and blots and the absence of pigment network were more likely associated to SLN positivity.

Since the 7th AJCC classification for melanoma introduced the number of mitoses as an additional important prognostic factor for upstaging thin melanoma [4], other studies have analysed their prognostic role in melanoma patients [5]. Yet no studies have been performed to evaluate a possible correlation between certain morphologic features of thin melanoma and the presence of mitoses as measured on histopathology.

The purpose of the current study is to evaluate the correlation between dermoscopic features and the presence of mitoses in a consecutive cohort of thin melanomas.

2. Materials and methods

We conducted a retrospective analysis of clinical, dermoscopic and histopathological characteristics of thin melanomas (equal or less than 1 mm in Breslow thickness) consecutively excised at a
referral pigmented lesion clinic from 2011 to 2014. Recorded clinical features of the patients included age, sex, date of diagnosis, and body site location of the primary tumour. Two dermatologists (SR and CL) jointly assessed all polarized dermoscopic images in blind for the presence/absence of dermal mitosis. Dermoscopic features included in the analysis were: presence of black, red and brown colour, atypical pigment network, atypical dots globules, blotches, peripheral streaks (considered positive when present in 25% of the pigmented lesion), blue-white veil, regression, shiny white lines, dotted vessels, polymorphous vessels, and ulceration [6,7]. Any disagreement was settled by consensus, including a third dermatologist (GA).

Histologically, the presence of mitosis has been described in accordance with Attis and Vollmer [8]. Mitotic figures were counted in a systematic manner by first choosing the area with the thickest dermal tumour mass, and then scanning the tumour from one edge to the other along one or more tracts parallel to the skin surface. All pathological melanoma slices have been systematically revised (SP).

### Table 1
Clinical features of melanomas according to presence of mitoses.

| GENDER | Mitoses = 0 (n = 131) | Mitoses ≥ 1 (n = 46) | p value |
|--------|-----------------------|----------------------|---------|
| F      | 41 (31%)              | 17 (37%)             | n.s.    |
| M      | 90 (69%)              | 29 (63%)             |         |

| BODY SITE | Mitoses = 0 (n = 131) | Mitoses ≥ 1 (n = 46) | p value |
|-----------|-----------------------|----------------------|---------|
| Head & Neck | 17 (13%)              | 7 (15%)              | <0.001  |
| Trunk     | 81 (62%)              | 14 (30%)             |         |
| Upper limbs | 19 (14%)              | 9 (20%)              |         |
| Lower limbs | 14 (11%)              | 16 (35%)             |         |

| AGE | Mitoses = 0 (n = 131) | Mitoses ≥ 1 (n = 46) | p value |
|-----|-----------------------|----------------------|---------|
|     | 56.5 +/- 15.58        | 60.28 +/- 16.26      | n.s.    |

2.1. Statistics

For basic statistical analysis, the absolute and relative frequencies of each clinical, dermoscopic and histological criterion were calculated. Significant differences in any clinical, dermoscopic or histological feature between melanomas with and without mitoses were evaluated by means of the Chi2-test, the Fisher test and the Spearman correlation coefficient.

Logistic regression was used to look at the association between dermoscopic features and the mitoses status. Linear regression was used to look at the association between dermoscopic features and the linear number of mitoses. All statistical tests were two sided and p values ≤ 0.05 were considered significant. The analyses were performed in STATA 12 (StatCorp LP, College Station, TX, USA).

3. Results

Dermoscopic images from 177 histopathologically proven melanomas with Breslow thickness ≤ 1 mm in 177 patients (119; 67% men) were analysed. Clinical and dermoscopic characteristics of the lesions are listed in Tables 1 and 2, respectively. The majority of lesions (131; 74%) had no mitosis at the histopathological examination, while 46 (36%) had at least 1 mitosis per mm² (range, 0–11 mitoses). The average Breslow thickness was 0.57 ± 0.22 (range 0.2–1 mm). Distribution of mitoses according to Breslow thickness is reported in Table 3. No differences were observed according to sex and age between melanomas with and without mitosis.

At logistic regression analysis, peripheral streaks (OR 4.11; 95% CI 1.94–8.71) and black colour (OR 4.70; 95% CI 2.28–9.68) were significantly associated to the presence of 1 or more mitoses, while atypical pigment network (0.30; 95% CI 0.15–0.61) and brown colour (OR 0.36; 95% CI 0.18–0.75) were associated to melanomas

### Table 2
Dermoscopic features of melanomas according to mitoses, (OR adjusted for Breslow thickness and age).

| Feature               | Mitoses = 0 (n = 131) | Mitoses ≥ 1 (n = 46) | OR (95% CI) | P value |
|-----------------------|-----------------------|----------------------|-------------|---------|
| Shiny white lines     | N 86 (66%)            | 29 (63%)             | n.s.        |         |
|                       | Y 45 (34%)            | 17 (37%)             |             |         |
| Blue-white veil       | N 91 (69%)            | 24 (52%)             | n.s.        |         |
|                       | Y 40 (31%)            | 22 (48%)             |             |         |
| Regression            | N 62 (47%)            | 26 (57%)             | n.s.        |         |
|                       | Y 69 (53%)            | 20 (43%)             |             |         |
| Dotted vessels        | N 116 (89%)           | 35 (76%)             | n.s.        |         |
|                       | Y 15 (11%)            | 11 (24%)             |             |         |
| Polymorphous vessels  | N 112 (85%)           | 38 (83%)             | n.s.        |         |
|                       | Y 19 (15%)            | 8 (17%)              |             |         |
| Dermoscopic ulceration| N 129 (98%)           | 44 (96%)             | n.s.        |         |
|                       | Y 2 (2%)              | 2 (4%)               |             |         |
| Atypical pigment network | N 30 (23%)         | 23 (50%)             | 0.30 (0.15–0.61) | 0.001  |
|                       | Y 101 (77%)           | 23 (50%)             |             |         |
| Atypical dots globules| N 87 (66%)            | 26 (57%)             | n.s.        |         |
|                       | Y 44 (34%)            | 20 (43%)             |             |         |
| Blotches              | N 90 (69%)            | 28 (61%)             | n.s.        |         |
|                       | Y 41 (31%)            | 18 (39%)             |             |         |
| Peripheral streaks    | N 110 (84%)           | 26 (57%)             | 4.11 (1.94–8.71) | <0.001 |
|                       | Y 21 (16%)            | 20 (43%)             |             |         |
| Black colour          | N 91 (69%)            | 15 (33%)             | 4.70 (2.28–9.68) | <0.001 |
|                       | Y 40 (31%)            | 31 (77%)             |             |         |
| Brown colour          | N 30 (23%)            | 22 (48%)             | 0.36 (0.18–0.75) | 0.006  |
|                       | Y 101 (77%)           | 24 (52%)             |             |         |
| Red colour            | N 102 (78%)           | 31 (67%)             | n.s.        |         |
|                       | Y 29 (22%)            | 15 (33%)             |             |         |
without mitoses (Fig. 1). All the data included were adjusted for Breslow thickness and age of the patients. Multicollinearity between variables was tested with the variance inflation factor without significant results.

Black colour (\(\beta = 1.62, p < 0.001\)) and streaks (\(\beta = 1.45, p < 0.001\)) were also associated to the increasing number of mitoses at linear regression, while atypical network (\(\beta = -1.12, p = 0.002\)) and brown colour (\(\beta = -0.91, p = 0.012\)) were inversely associated to the number of mitoses when adjusted for age and Breslow thickness.

4. Discussion

In the last AJCC staging system, mitotic rate and ulceration have been considered upstaging factors in melanoma thinner than 1 mm, thus influencing the decision to perform SLNB biopsy [4]. The invasive technique of sentinel lymph node biopsy (SLNB) has become the standard procedure to detect occult regional node metastasis, and has a value for staging and prognosis in clinically localised primary melanomas [9,10]. In our study, aimed to identify dermoscopic features that may predict the presence of mitoses in thin melanomas, black colour and peripheral streaks were found associated to an increasing chance of detecting mitoses.

Black colour has been reported to be more associated to thick nodular melanoma. On confocal microscopy and histology, black blotches result from a total filling of the epidermis by an upward migration of nests of melanocytes and pagetoid melanocytes as single cells and clusters. Black dots/globules also correspond to the upward migration of nests melanocytes in the epidermis and pagetoid spread, but with sparing of intervening areas of the epidermis. Overall, the presence of black colour is generally related to pigment-containing melanocytes in close proximity to the surface of a thinned epidermis, suggesting that a bulging proliferation of dermal melanocytes beneath a thin epidermal layer could precede ulceration [9]. Although this feature is usually described in relation to nodular melanoma, in this study we can speculate regarding its morphology inside the lesion and not to the histotype of the tumour. Thus, the presence of black colour is a dermoscopic marker of a pre-ulcerative stage and although it is not directly linked to the presence of mitosis on histopathology, it’s a marker of aggressiveness.

Peripheral streaks represent the second dermoscopic features predicting high mitotic rate. This feature is usually detected in lesions typified by a fast-growing attitude such as Spitz/Reed naevi and melanomas. In the latter, a recent study has proven that peripheral streaks are also linked to a specific c-KIT mutation [11]. Our results confirmed that peripheral streaks in thin melanomas are a dermoscopic feature related to tumour aggressiveness [12].

![Table 3: Mitoses distribution according to Breslow thickness.](image-url)

| Mitoses \(\geq 0\) (n = 131) | Mitoses \(\geq 1\) (n = 46) | Total |
|---|---|---|
| 0.1 | 0 | 0 | 0 |
| 0.2 | 4 | 1 | 5 |
| 0.3 | 16 | 3 | 19 |
| 0.4 | 43 | 4 | 47 |
| 0.5 | 25 | 6 | 31 |
| 0.6 | 0 | 3 | 3 |
| 0.7 | 25 | 7 | 32 |
| 0.8 | 8 | 8 | 16 |
| 0.9 | 7 | 7 | 14 |
| 1.0 | 3 | 7 | 10 |
| tot | 131 | 46 | 177 |

**Fig. 1.** A. Melanoma of 0.5 mm in thickness without mitoses reveals only brown colour and atypical pigment network; B. Melanoma 0.5 mm with mitoses shows black colour and peripheral streaks; C. Melanoma of 0.9 mm Breslow thickness and no mitoses showing brown colour and atypical pigment network; D. Melanoma 0.9 mm with mitosis exhibiting black colour and peripheral streaks.
since the presence of mitoses is a direct sign of tumour proliferation.

In our study, the features associated to melanomas without mitoses were brown colour and atypical pigment network. In previous studies, the presence of brown colour has been reported to be associated with slow growing melanomas [13–15] and a reticular pattern has been found significantly associated to thin melanomas [8,15]. It is well known that the pigment network correlates with the presence of pigmented rete ridges on histology whereas more aggressive melanomas usually (i.e. nodular type) lose the rete ridges because of tumour progression. The absence of rete ridges in histopathology corresponds to the lack of pigment network in dermoscopy. In other words, the more the tumour tends to proliferate (i.e. presence of mitoses) the less it tends to show pigment network.

Our findings might suggest to directly perform a wide excision when a patient exhibits a dermoscopically typical thin melanoma with features suggestive of absence of mitoses instead of a limited excision followed by wider excision after obtaining the histopathological diagnosis.

The main limitations of this study are the following: the relatively limited number of patients, its retrospective design and the fact that it was performed in one single tertiary referral institution.

In conclusion, the present study demonstrates that specific dermoscopic variables (black colour and peripheral streaks) are positively associated with thin melanomas with mitoses while others (brown colour and atypical pigment network) are more associated to a less aggressive phenotype.

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