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DERMOSCOPY AND HISTOPATHOLOGY CORRELATIONS IN MELANOMA - CAN DERMOSCOPIC CRITERIA PREDICT THE SEVERITY OF MELANOMA?

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ABSTRACT

Dermoscopy-histopathology correlations have been studied for a few years now. While difficult to assess, the pathology correspondence of each dermoscopic criterion would offer great insight into the melanoma evolution. We attempted to take a closer look into the melanoma dermoscopic clues and the severity of the tumor. In order to determine a link between the 10 specific melanoma criteria and its stage we searched for correlations between dermoscopy and classic histopathologic parameters such as Breslow thickness, Clark index, mitosis index, the presence of ulceration, regression, inflammatory infiltrate, lympho-vascular invasion, cases satellite tumor nodules or perineural invasion. We evaluated the dermoscopy and pathology of 58 melanocytic tumors (35 melanomas, 6 atypical nevi and 17 common nevi) in a prospective study. The atypical network proved to be correlated with thinner and more superficial melanomas. On the other hand, vascular dermoscopy patterns (dotted, polymorphous, serpiginous vessels, milky red areas and red globules) were seen generally in thicker, more invasive and more advanced melanomas. The results were consistent with other studies performed in the past.

KEYWORDS: *melanoma, dermoscopy, histopathology, severity, Breslow index*

INTRODUCTION

Dermoscopy nowadays is a mandatory diagnostic device when evaluating pigmentary tumors. It has proven to be of valuable assistance when trying to distinguish a malignant tumor from a benign one for years now [1]. It was first used especially for melanocytic lesions, but throughout the years there have been described also criteria for other types of dermatologic tumors and inflammatory diseases. It has even been developed for mucosal and hair conditions. It is safe to say that it can be compared to the stethoscope for the cardiologist, being present in every dermatologist's office all over the world [1].

The dermoscopic criteria are still being perfected by experts in this field. There have been created a lot of algorithms when analyzing a melanocytic lesion to determine its nature, but the perfect one hasn't been yet described. Examples of some of these algorithms are the ABCD rule [2], the CASH algorithm [3], the three-point checklist [4], the seven-point

checklist [5], BLINCK algorithm [6] and the list can continue. All of them have tried to facilitate the recognition of melanoma but there still isn't one that can distinguish with 100% certainty all of the malignant melanocytic tumors. However, in the last few years, clues of incipient melanomas have been characterized bringing us closer and closer to early detection of these tricky malignant tumors [7], [8].

In order to take a closer look to melanomas, researchers have tried to find histopathologic correspondence for every dermoscopic criterion [9] – [11]. This is useful in explaining why some elements appear in some tumors and others don't and also it can assist in detecting early melanomas only by looking with the dermoscope. It is the most aggressive cutaneous malignancy, being responsible for a high mortality, even though its prevalence is only up to 5% of all skin tumors [12], [13]. If we can predict the melanoma thickness with dermoscopic criteria we will then be able to decide the excision margins from the beginning and to predict the outcome of the tumor. Early detection and treatment of melanomas can improve the patient prognosis and reduce considerably the risk of metastasis formation.

MATERIALS AND METHOD

We have enrolled 58 patients with melanocytic lesions during a 2-years period in Colentina Clinical Hospital in Bucharest, Romania between 2017 and 2019. After receiving the ethic committee consent and the informed consent of each patient, we took clinical and dermoscopy photos, the lesions were excised and histopathological examination was performed. The data was stored in Microsoft Excel and the statistical analysis software used was IBM SPSS Statistic Data Editor.

Dermoscopy was performed using DermLite dermoscopes (ProHr, Hybrid and DL4) with polarized and/or nonpolarized light and the digital photos taken were then analyzed on the computer by three dermatologists. We described the lesions using the 10 melanoma specific criteria (Table 1) [14]. Histopathologic classic parameters were used as indicators of melanoma prognosis and severity and were evaluated along with the dermoscopic features. We applied nonparametric tests such as Pearson, Spearman and Mann-Whitney U tests and analyzed the r-square and p-value in order to verify the statistical significance of the results.

RESULTS

Out of the 58 melanocytic lesions 35 were melanomas, 6 atypical nevi and 17 common nevi. Half of the patients were female (29) and half male (29). The mean age of the patients was 55.21 years with the youngest patient having 18 years and the oldest being 86 years-old.

The mean Breslow index was 3.1 mm for the 35 melanomas assessed. 40% of the melanomas had Breslow thickness under 0.8 mm, while 48.6% were more than 2 mm thick, only 2.9% 0.8-1 mm and 8.6% 1-2 mm. The melanoma cases were predominantly Clark index IV (65.7%), implying deeper involvement of the melanoma cells in the analyzed tumors (Clark I - 14.3%, Clark II - 2.9%, Clark III - 11.4%, Clark V - 5.7%) (Figure 1). Another important histopathologic criterion is the number of mitoses. Out of all the studied melanomas 65.7% had more than 1 mitosis and 34.3% had 0 or 1 mitoses. All of the melanomas with 1 or less mitoses had Breslow thickness under 1 mm in contrast with only 8.7% of the melanomas which had more than 1 mitosis, the rest being thicker than 1 mm.

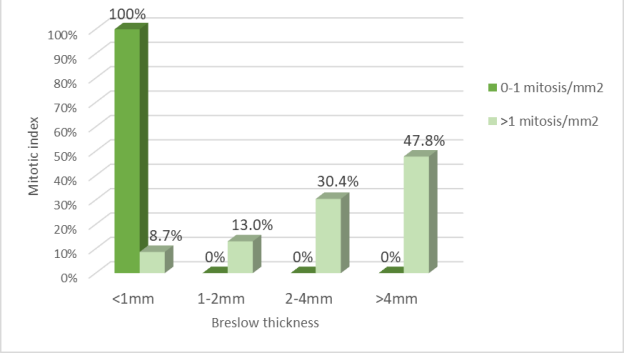

Figure 1 – Distribution of mitotic index according to Breslow thickness

The tumor infiltrating lymphocytes were present in 74.3% of the melanomas, out of which 68.2% were non-brisk and 31.8% brisk. 36.4% of the studied melanomas revealed a certain proportion of tumor regression. The enrolled melanomas displayed in 18.7% of the cases lympho-vascular invasion, in 9.4% of the cases satellite tumor nodules, 34.3% presented ulceration and none of the melanomas had perineural invasion.

1. Atypical network	Changes in the pigment network - thicker lines and more narrow pigment holes
2. Streaks	Peripheric lines which are symmetric or asymmetric and/or pseudopods represented by peripheric lines with globular ending
3. Negative pigment network	Discolored/hypopigmented lines forming a network surrounded by hyperpigmented/brown areas
4. Crystalline structures	Short shiny white lines which can be seen only with polarized light
5. Dots and globules	Colored pigment dots (black, brown, gray)
	Colored pigment globules, bigger than the dots, distributed anywhere on the lesion (black, brown, gray)
6. Blotch	Structureless areas gray/brown/black which are symmetrically/asymmetrically distributed on the lesion
7. Brown peripheral structureless areas	Light brown structureless areas seen in the periphery of the lesion
8. Blue-white veil overlying raised areas	White color over a structureless blue area seen in raised portions of the lesion
9. Regression structures	Dermoscopic structures which suggest that the lesion is disappearing
Blue-white veil overlying macular areas	White color over a structureless blue area seen on a flat lesion
Scar-like areas	Structureless white area, lighter in color than the normal skin surrounding the lesion
Peppering	Also known as granularity - multiple blue-gray dots, smaller than 0.1mm
10. Atypical vascular structures	Chaotic vessels with multiple aspects in the lesion
Dotted vessels	Small dotted blood vessels
Serpentine vessels	Tortuous blood vessels
Milky-red areas	Globules or bigger areas of diffuse red-white color corresponding to a raised/elevated part of the lesion
Red globules	Red globules often near milky-white areas
Polymorphous vessels	Vessels of different morphologies present in the same lesion, mostly the combination of dotted and linear-irregular vessels

Table 1 – The 10 melanoma specific criteria and their description

As far as dermoscopy is concerned, the 10 melanoma specific clues were evaluated in relation to histopathologic parameters. The negative network was present in older patients ($p=0.039$, $r=0.372$ of moderate statistical power) and in melanomas which showed ulceration ($p=0.039$, $r=0.4$). Atypical network correlates statistically with smaller Breslow thickness ($p=0.024$, $r=0.41$), with smaller Clark index ($p=0.029$, $r=0.392$) and with a smaller mitotic rate ($p=0.026$, $r=0.401$). It is also present more in tumors without ulceration ($p<0.0001$, $r=0.657$). The presence of peppering was correlated with the presence of regression in melanoma with a $p=0.033$ in Pearson test ($r=0.397$) and also with the presence of scar-like areas in dermoscopy ($p<0.0001$, $r=0.488$). Scar-like areas were statistically correlated with a smaller Breslow index ($p=0.021$, $r=0.412$) and with a smaller Clark index ($p=0.032$, $r=0.386$) and was present in regressed melanomas ($p=0.33$, $r=0.397$).

Other dermoscopic criteria which were found to have statistical significance were the atypical vessels (Figure 2) – almost all of them were positively correlated with Breslow index. Polymorphous vessels were positively correlated with Breslow index ($p<0.0001$, $r=0.589$), mitotic index ($p=0.009$, $r=0.453$), with the presence of ulceration ($p=0.005$, $r=0.519$) and lympho-vascular invasion ($p=0.035$, $r=0.393$). Serpiginous vessels were seen to be present in melanomas with thicker Breslow index ($p=0.013$, $r=0.443$), with bigger Clark index ($p=0.012$, $r=0.438$), with more than 1 mitosis ($p=0.007$, $r=0.465$) and with ulcerated tumors ($p=0.002$, $r=0.559$). Also, it was found a moderate correlation if the melanomas showed lympho-vascular invasion ($p=0.034$, $r=0.395$) and satellite tumor nodules ($p=0.044$, $r=0.377$). Dotted vessels were statistically associated with Breslow thickness ($p=0.003$, $r=0.513$), Clark index ($p=0.049$, $r=0.351$), mitotic index

(p=0.009, r=0.453), lympho-vascular invasion (p=0.035, r=0.393) and with the presence of ulceration (p<0.0001, r=0.684). Milky red areas and red globules on dermoscopy were both present in melanomas with thicker Breslow index (p=0.048, r=0.358, respectively p=0.026, r=0.394), while red globules were correlated also with the presence of more than 1 mitosis in the tumor (p=0.009, r=0.453).

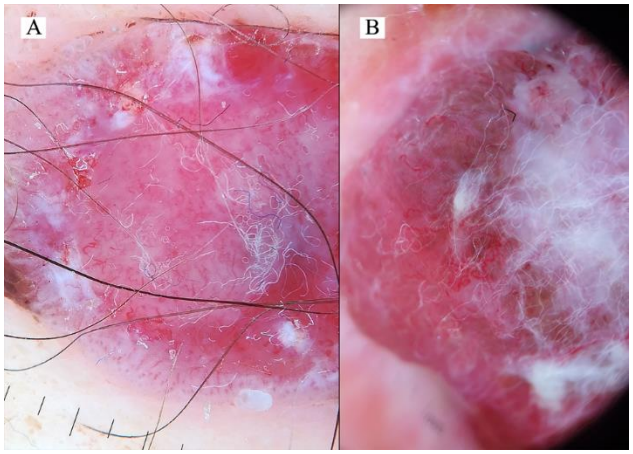

Figure 2 – A: Dermoscopy of melanoma (BI = 2.4 mm, CI=IV, MI = 6/mm^2) with polymorphous vessels, red globules, milky-red areas, serpiginous and dotted vessels; B: Vascular atypia on a melanoma dermoscopy (BI = 7 mm, CI=IV, MI = 19) consisting of mainly polymorphous and serpentine vessels

DISCUSSION

In the last years, clinicians have been able to detect far more melanomas than in the past with the use of dermoscopy and also by catching them in earlier stages which is a huge step for these malignant tumors [15]. When caught in earlier stages, patients with thinner melanomas have a better prognosis and survival rate [16].

Out of all the 10 melanoma specific clues, only some of them proved to be statistically significant in our cohort of patients. The most frequent criteria present in melanomas was the atypical network which appeared on the dermoscopy of 68% of the malignant tumors (24/35). The proportion is comparable to that of the study conducted by Argenziano et al in 2011 [17]. We observed that this dermoscopy finding was present more in case of incipient melanomas being associated with thinner Breslow, smaller Clark index and with the presence of 1 or less mitoses on the pathology examination. Therefore, we can state that changes in the normal pigment network are some of the first discoveries on dermoscopy and should be taken into consideration when present in a pigmented tumor. Atypical network is one of the most used dermoscopy criteria in algorithms to detect melanoma such as the three-point checklist [18], the seven-point checklist [17].

The dermoscopic negative network was found to be correlated with the presence of ulceration in the pathology report which suggests that it can appear in more advanced melanomas. In our cohort, melanoma severity grew with age and also the negative network was correlated with advanced ages, thus confirming the idea that this dermoscopy clue is present in more aggressive tumors. For this criterion, findings have been contradictory and so there is no consensus of a relevant histopathologic correlation yet described [9], [19] – [21].

Both peppering and scar-like areas were associated with regression in the tumors which is relevant since in past studies these criteria were observed to be representing areas of thin epidermis with fibroplasia and leukocytes [9], [22]. Still there is no consensus on the significance of this process on whether it is beneficial or not. The immune system is trying to attack the tumor and by doing so the pigment progressively disappears leaving marks such as brown-gray granulation (incomplete regression) and white areas resembling a scar (complete regression). However, this can also mean that the tumor is in an advanced stage and has a worse prognosis in some cases. In our melanomas, scar-like areas were present in thinner tumors (smaller Breslow index) and less invasive (smaller Clark index).

Vessels are an important factor in tumors, most of them being well vascularized because of their rapid growth. Especially in melanomas with vertical growth, nodular and amelanotic/hypomelanotic melanomas, where nodules can be seen above the skin, vessels will be visible on dermoscopy. Depending on the type of vessels several conclusions can be drawn.

Figure 2 – Picture (A) Dermoscopy of melanoma (BI=2.4mm, CI=IV, MI=6/mm2) with polymorphous vessels, red globules, milky-red areas, serpiginous and dotted vessels; Picture (B) Vascular atypia on a melanoma dermoscopy (BI=7mm, CI=IV, MI=19) consisting of mainly polymorphous and serpentine vessels

Atypical vessels were seen predominantly in advanced melanomas with a thicker Breslow index, irrespective of the type of vascular pattern. Other studies showed the same conclusion, suggesting that the thicker the melanoma, the more types of vessel morphologies were present [23] – [25]. Dotted vessels can be a good clue for suspecting a melanoma, but it also can be seen in benign tumors so it is not a specific clue [26]. However, if dotted vessels are seen in lesions the suspicion of melanoma should be raised, especially if no other specific melanoma clue is present on dermoscopy and excision or at least biopsy should be taken into consideration [26], [27]. In our cohort of patients, the presence of dotted vessels was increased in thicker, deeper and more invasive melanomas and absent in common and dysplastic nevi.

According to other studies, the most frequent vascular patterns present in melanomas were linear-irregular vessels, dotted vessels and polymorphous vessels [23], [26], [28]. Polymorphous vessels represent more than one vascular pattern, but mainly consist of the combination between dotted and linear-irregular vessels in melanoma. In the tumors studied by us, this dermoscopic clue was seen to be positively correlated with thick, aggressive and invasive melanomas according to histopathology findings. This would mean that seeing polymorphic vascular structures suggests an advanced melanoma.

Serpentine or serpiginous vessels as the name suggests are tortuous vessels similar to a serpentine or a snake. They were positively correlated in our cohort with histopathologic criteria which show invasiveness and aggressiveness of the melanoma, appearing in thicker tumors with ulceration and more than 1 mitosis present. In other studies, this vascular morphology was seen not only in melanoma, but also in basal cell carcinoma [29], [30].

Milky-red areas are believed to contribute significantly to the recognition of melanoma, even though they are more rarely seen [26], [28]. In concordance to our study, milky red areas were present generally in melanomas with a thicker Breslow index [26]. Among the studied tumors in our cohort this criterion was more frequent than other vascular morphologies. They appeared in 40% of the melanomas (14 out of 35) in our study, in contrast to 4.7% of the melanomas (7 out of 150) in the study of Argenziano et al [26]. This criterion suggests an intense vascularization into the tumor playing a significant role in amelanotic areas of the melanoma [24]. Sometimes, associated with these milky-red areas, there can be seen red globules on dermoscopy which most probably accentuate the increased blood flow in the melanomas.

CONCLUSION

Our study demonstrates that certain dermoscopic features can be of real use in our daily practice for stratifying the risk of melanoma before excision. While dermoscopic criteria such as atypical network suggests an early melanoma, vascular atypia is a sign of a more advanced melanocytic tumor. When polymorphous, dotted, serpentine vessels and milky-red areas are present in a melanoma, our dermoscopy-histopathology correlations suggest that fast and wide excision is the best course of action since there is most probably an aggressive type of melanoma. Peppering and scar-like areas are reconfirmed as regression structures in our study as they were significantly correlated with the presence of regression on the pathology report. Negative pigment network was seen in older ages and in melanomas with ulceration, thus in more advanced tumors. Our findings bring the knowledge about dermoscopy and severity of melanoma a step closer and with more similar studies we will be able to formulate algorithms that can predict melanoma stages just by looking into the dermoscope.

Out of the 10-melanoma specific dermoscopy criteria, only some of them proved to have statistical significance in our group of patients. One was related to incipient melanomas while other dermoscopic clues predicted a more advanced type. In order to have more precise results and a better understanding of the situation more studies with larger cohorts of patients are needed.

It is of paramount importance to keep studying this field in order to be able to predict with more precision only by dermoscopy the melanoma stage. This would facilitate and bypass the prolonged course of action of the histopathology examination and by that in the

future it might be able to quicken one's correct treatment initiation.

Authors' contributions: All the authors had equal contributions.

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