Original Paper

The Importance of Dermoscopy in Early Recognition of Melanoma in Situ

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ABSTRACT: Early recognition of melanoma in situ (MIS) is an ongoing challenge in dermatology. It rarely arises 'de novo', most frequently resulting due to the transformation of an atypical nevus. The diagnostic criteria for MIS are diverse dermoscopy being the most used and it has a sensitivity of 83% and a specificity of 69% in detecting melanomas. The main objective of our study was to establish the sensitivity and the specificity of each of the 7-point checklist criteria used to differentiate melanocytic nevi from in situ malignant melanoma. The study group included 200 patients, aged over 18 years, with atypical pigmentary nevi after clinical aspects that presented changes in clinical appearance (shape, color, dimensions) during the last 6 months. On each patient we used the 7-point checklist of Argenziano (C1-C7). The study was performed at the Medical Center Dr. Ianosi, in Craiova between January 2016 and September 2018 and it was used Molemax HD computerized dermatoscope. The C1÷C3 criteria are significantly relevant in establishing the diagnosis of MIS in comparison with the diagnosis of nevus, unlike the C4-C7 criterion that is not definitely relevant for confirmation of the MIS diagnosis. There are no enough specific dermoscopic criteria to differentiate MIS from atypical nevus.

KEYWORDS: Melanoma in situ, atypical nevi, dermoscopy

Introduction

Melanoma in situ (MIS) is a neoplasm which cannot be easily detected but its treatment leads to complete remission. MIS is the very earliest stage of a skin cancer called melanoma, the cancer cells are found only in the outer layer of skin (epidermis) and have not grown into any other layers [1].

Patients with MIS are considered at very low risk for local recurrence or for regional and distant metastases. Early detection of MIS increases survival from melanoma, with treatment, patients with Stage 0 melanoma have a 5-and 10-year overall survival rate of 99%-100% [1,2,3].

In this condition, it is very important to diagnose earlier this cancer, but the recognition of MIS is a constant challenge in dermatology. MIS may be suspected clinically or by dermoscopy but the diagnosis is confirmed by histological examination. The frequency diagnosis of this disease has risen due to the constant use of *in vivo* tools such as dermoscopy (epiluminescence microscopy) This early detection is because dermoscopy reveals the natural asymmetry of melanoma before it becomes clinically evident. It represents a method that evaluate the superficial structures of the skin but this test should be a valuable diagnosis tool if it is used by experimented dermatologist [1,2].

Dermoscopy has a sensitivity of 83% and a specificity of 69% in detecting melanomas [3,4].

There are many algorithms used such as ABCD rules, Menzies algorithm, the algorithm of Argenziano (7-point checklist) and 3-point checklist [4,5,6].

Despite it all, until now, there have been no specific dermoscopic feature that can establish with certainty the diagnosis of MIS, these criteria can be found in atypical nevus or invasive melanoma, also [6].

The main objective of this study was to establish the sensitivity and the specificity of each of the 7-point checklist criteria of Argenziano in order to distinguish atypical melanocytic nevi from in situ malignant melanoma.

Material and Methods

The authors performed a prospective study between January 2016 and September 2018 that included 200 patients, aged over 18 years, with atypical pigmentary nevi after clinical aspect, but that presented changes in clinical appearance (shape, color, dimensions) during the last 6 months.

Each subject was examined clinically and dermoscopically with a 30x Molemax HD computerized dermatoscope. For the latter, we used the 7-point checklist of Argenziano that consists of: C1-atypical pigmented network, C2-blue whitish veil, C3-atypical vascular pattern, C4-irregular dots/globules, C5-irregular streaks, C6-irregular blotches and C7-regression structures.

Exclusion criteria:
- patients with folliculitis and perinevic eczema
- associated malignancy except a possible cutaneous cancer
- de novo pigmented tumours

In spite of the dermoscopic features, all the lesions were surgically removed and histological examined. Immunohistochemical exams were performed at 144 patients (72%).

This study was conducted in the Medical Center DR Ianosi (Craiova, Romania). Each patient over 18 years of age signed the written informed consent in accordance with the World Medical Association Declaration of Helsinki (1975) and approved by the Institutional Ethics Committee of the Medical Center DR Ianosi (No.446/12 December 2015).

Statistical analyzes

Quantitative variables were presented as mean±standard deviation (SD), standard errors and the confidence levels (95%), and qualitative variables as frequency and percentage.

Chi-square test and student t-test were used whenever appropriate. P value less than 0.05 was considered significant.

Results

A total of 200 patients (97 males; 103 females) records were reviewed in this study. According to histopathological results there were 37 patients with in situ malignant melanoma-20 males (54.05%) and 17 females (45.94%) and 163 patients with atypical pigmented nevus-77 males (47.24%), 86 females (52.76%).

The mean age of the patients was 50.74 years old (±14.09), and their age range was between 21 and 79 years.

There was no difference between the two genders in regard to the frequencies of any of the diagnoses.

In our study, for MIS diagnostic the most relevant criteria were the first three: C1-atypical pigment network, C2-blue whitish veil and C3-atypical vascular pattern. We didn't find any of these criteria in patients with atypical nevus. C1-atypical pigment network was found in our 37 patients with melanoma (43,24% of cases), C2-blue whitish veil in 40,54% and C3-atypical vascular pattern at 45,94% of MIS patients (p<0,05%) (Table 2), so we assumed that these criteria could be considered as major criteria in the diagnosis of malignant melanoma.

Sensitivity and specificity were higher for MIS for the first three criteria in this study compared with the last four: 87,33% with 90,81% for C1, 76,67% with 90,27% for C2 and 85,88% with 88,19% for C3 respectively.

C4-irregular dots/globules were found in 48,64% of patients, but also, we discovered it in 22,22% of patients with NEV (Table 2).

Sensitivity was 42,85% and specificity 51,04% for this criterion for MIS diagnosis (as shown in Figure 2 and 3).

C5-irregular streaks was found in 56,75% of the patients with MIS and in only 22,22% of the patients with NEV (Table 2), with a sensitivity for MIS diagnosis of 55,48% and a specificity of 58,87% (Figure 2 and 3).

The sixth criterion, C6-irregular blotches was found, in our study, in 54,06% of patients with MIS and in 26,67% of patients with NEV (Table 2). We calculated a sensitivity of 40,62% and a specificity of 48,92%. C4, C5 and C6 criteria aren't specific for MIS, in our opinion, because were found in patients with NEV, also; the percentages were smaller than first three criteria and the specificity was also smaller than major ones.

C7 criterion-regression structures wasn't much more relevant for MIS diagnosis compared with NEV (37,8%) (p=0,402581). Sensitivity for this criterion was 42,30% and specificity were 53,62% (Table 3 and 4).

Table 1 offers the average and standard deviation for the criteria C1 to C7. The standard errors and the confidence level for these criteria are, also, listed in Table 1.

Table 1. The average, standard deviation, standard errors and the confidence levels for the criteria C1 to C7.

	C1	C2	C3	C4	C5	C6	C7
AVERAGE	0.732432	0.625405	0.689459	0.486486	0.56756757	0.540541	0.378378
ST. DEV.	0.502247	0.497743	0.505228	0.506712	0.5022472	0.505228	0.491672
ST. ERR.	0.082569	0.081828	0.083059	0.083303	0.082569	0.083059	0.08083
Confidence level (95%)	0.167458	0.165956	0.168451	0.168946	0.1367458	0.168451	0.163932

The values obtained for the seven diagnostic of in situ malignant melanoma, in our patients group are presented below in Figure 1.
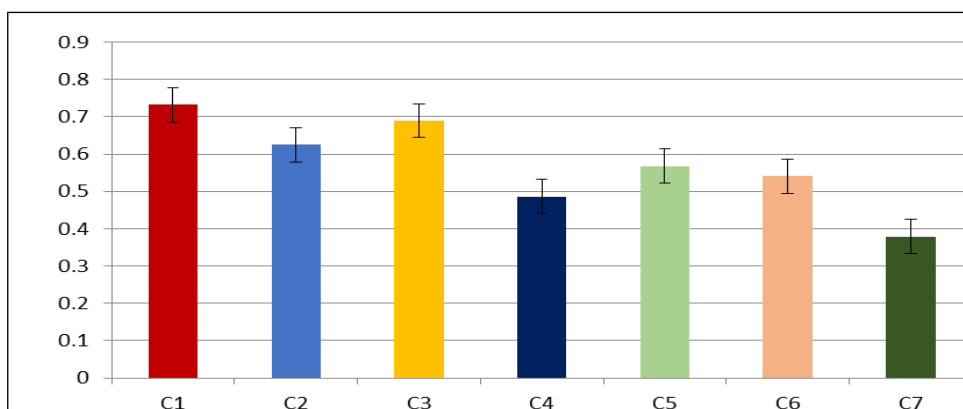

Figure 1. The criteria C1-C7 in the diagnostic of MIS's results. Error bars represent standard deviation.

Table 2 presents the frequencies of appearance of the criteria C1÷C7 for each diagnostic.

Table 2. Frequency of criteria C1-C7 in the diagnostics of MIS and NEV results.

Diagnostic	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**
MIS	16 (43.24%)	15 (40.54%)	17(45.94%)	18(48.64%)	21 (56.75%)	20 (54.05%)	14 (37.83%)
NEV	0 (0%)	0 (0%)	0 (0%)	10(22.22%)	10 (22.22%)	12 (26.67%)	12 (26.67%)

The specificity and sensitivity of the criteria C1÷C7 in the diagnosis of MIS is presented in Table 3. The criteria C1÷C3 are significantly relevant in establishing the diagnostic of MIS.

The appearance of other criteria is not definitely relevant for confirmation the diagnostic, but we cannot exclude them for the MIS diagnosis by counting the difference of frequency in MIS patients compared with NEV.

The sensitivity and specificity for the criteria C1-C7 are presented in Figures 2 and 3.

These shows a higher sensibility and, also, specificity, for the first three criteria for the diagnosis of in situ malignant melanoma.
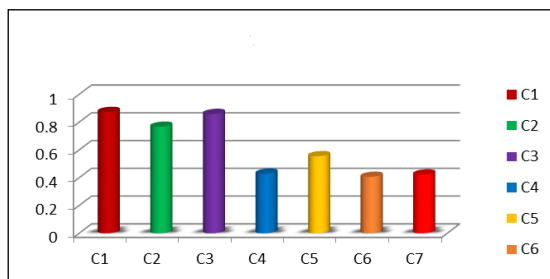

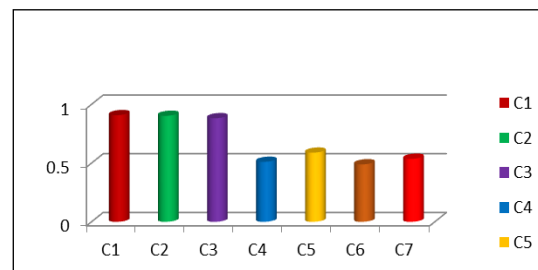**Figure 2. Sensitivity for the criteria C1÷C7.**

Figure 3. The specificity for the criteria C1÷C7.

Table 3. The sensitivity and specificity of the criteria C1÷ C7 in the diagnosis of MIS.

	C1	C2	C3	C4	C5	C6	C7
Sensitivity (Sn)	0.873333	0.766667	0.858824	0.428571	0.554839	0.40625	0.423077
Specificity (Sp)	0.908124	0.902703	0.881967	0.510465	0.588757	0.489286	0.536207

Discussion

Melanoma in situ (MIS) is a cutaneous malignancy of the melanocytes limited to the epidermis. There are several clinical subtypes of in situ melanoma: lentigo malign, superficial spreading, acral lentiginous and mucosal. The histopathologic correlation reveals a pagetoid spread of the tumour cells due to a proliferation of single or multiple groups of atypical melanocytes along the basal epidermal layer or all over the epidermis into the granular or horny layers or both [4,5].

The incidence of melanoma in situ is rapidly increasing compared to other cancer including the incidence of invasive melanoma [6,7].

Also, in regard to the anatomic distribution, the most common sites for MIS are head and neck [4].

Regarding the gender distinctions in melanoma in situ development, it seems that females are more prone to develop melanoma in situ on the lower limbs as compared to males [8,9,10,11].

A possible explanation may be due to the different exposure to carcinogenic agents in clothing/hair style, inside versus outside occupation and sun-seeking behavior between males and females.

The progress of very sensitive diagnostic techniques, especially dermoscopy, makes it possible to distinguish melanoma in early stages (in situ) [6,7].

This diagnostic technique increases the diagnosis veracity of pigmented skin lesions, mainly improving the diagnosis of MIS despite of only few specific dermoscopic features. Furthermore, dermoscopy is more accurate with 10-27% in comparison with the naked eye examination when referring to melanoma [12,13].

There are numerous algorithms used for the last-mentioned purpose such as pattern analysis, ABCD rules, Menzies algorithm, the algorithm of Argenziano (7-point checklist) and 3-point checklist [12,14,15,16].

The seven-point checklist, introduced in 1998, has high sensitivity and specificity, therefore being most commonly used for all pigmented tumours [14].

Several studies were conducted with the aim to establish some dermoscopic criteria for MIS. One study performed by Lallas et al. [17] in 3 centers specialized in diagnosis and management of cutaneous cancer included 1285 persons with histopathological diagnosis of MIS or other pigmented tumours that were histopathological diagnosed or followed up for minimum 1 year, one quarter were MIS, almost half were nevi and the rest were represented by other precancerous and non-melanoma skin cancers, Reed nevi and invasive melanomas (7.9%). There are three predominant dermoscopic criteria for MIS: regression (92.9%), atypical network (85.5%), and irregular dots and/or globules (50.2%). Furthermore, the multivariate analysis pointed that there were 5 positive dermoscopic indicators of MIS: irregular hyperpigmented areas, regression, atypical network, prominent skin markings and angulated lines. From these all, in comparison with surgically removed nevi, only asymmetrical hyperpigmented areas and pronounced skin markings remained powerful MIS indicators [17].

Another retrospective clinical study [18] included 37 patients with MIS showed that the most relevant dermoscopic criteria for MIS were: the blue-whitish veil (78%), grey-blue areas (73%), black dots (62%), and irregular extensions and branched streaks (62%). Other features like brown globules (57%), irregular pigment network (54%), pseudopods (54%), and depigmentation (51%) were also present in approximately half of the lesions. Some other dermoscopic feature such as white scar-like areas and linear and/or dotted vascular patterns that are commonly found in cases of invasive melanomas were not present. Dermoscopic criteria appear regardless of MIS size [18].

Another study run by S. Bassoli et colab. [19] tried to determine the prevalence and expansion of 11 dermoscopic indicators of regression assessing the images of 111 MIS, excised between the years 2003-2009 in Department of Dermatology of the University of Modena. The dermoscopic feature were: regression, grey blue areas (structureless, globular, reticular), peppering, white areas, blue-whitish veil, pink areas, light brown areas, regression of dermoscopic (fading of net, globules, or pigmentation giving rise to light brown areas or small structureless areas within a structured area). The result showed that the regression structures (grey-blue areas, white areas, peppering, and/or blue-whitish veil) ranked first with 80.1% of the lesions. Also, the same percentage presented regression of dermoscopic structures and light brown areas. Second were the grey-blue areas (74.7%), followed by structureless areas with a pinkish hue (fibrosis) (50.4%) in half of the cases while peppering was

present in one third (30.6). Lastly, the white areas were seen in approximately 10% of the cases whereas the blue-whitish veil in 1.8%.

According to this study, only 2 dermoscopic features (the reticular pattern of blue regression and light brown areas) can be taken into account as a vital discriminator and a predictable indicator of MIS [19].

Regarding the dermoscopic and histopathological appearance of clinically suspected melanocytic lesions a new term, "mistletoe sign" was described. This feature appears as of many, well-defined areas, consisting of irregular, branched structures, similar to pseudopods, arising from an overall reticular or homogenous pattern, looking like the mistletoe [20].

The most recent studies show that in comparison to atypical nevi, MIS appears more often larger in size, with a peculiar network extending to more than 50% of the lesion, the simultaneous presence of different type of networks and more spread reticular grey-blue regression areas located centrally and peripherally in the lesion [21].

Seidnari et al. [1] described 8 dermoscopic subtypes of MIS. The mostly seen were the following: reticular grey-blue (27.2%), reticular pattern (21.1%), multicomponent (20.2%) and those rarely occurring: island (10.5%), spitzoid (7%), the inverse network (6.1%), blue globules network (5.3%) and globular network (2.6%).

Another highly-sensitive predictor for MIS is the dermoscopic island [22].

It was described as a well-demarcated area, with a homogeneous dermoscopic pattern which differs from the remainder of the pigmented lesion [22].

This characteristic was seen as a potential early sign of transformation of a nevus into a melanoma due to its presence in situ melanomas (10.4%), in atypical dermoscopic nevi (3.1%) and in invasive melanomas (4.1%).

Another dermoscopic sign of the melanoma is the "mushroom-cloud sign" [23].

It is described as a hyperpigmented area spread in one direction, outside the limits of the lesion, and the plume underneath exhibits the stalk-like projection [24].

As we can observe in these clinical studies, aren't standardized dermoscopic criteria for MIS diagnosis. In according with our study, C1-atypical pigmented network, C2-blue whitish veil, C3-atypical vascular pattern criteria are specific for in situ melanomas, never find them in patients with NEV.

C4-irregular dots/globules, C5-irregular streaks, C6-irregular blotches and C7-regression structures aren't specific for melanomas being find in patients with NEV too, but in a small percentage.

Conclusions

Melanomas in situ are challenging to diagnose due to the absence of well-defined dermoscopic characteristics.

There are no definitive differentiating dermoscopic criteria which can undoubtedly recognize atypical nevi from melanoma in situ.

In a future, it is required a further research for predictors of MIS and clinically suspected skin lesions in dermoscopy.

Acknowledgment

Conflict of interests

None to declare.

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