

Clinical and Dermatoscopic Signs of Micromelanoma - A Review of the Literature

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Abstract: *Introduction:* Micromelanoma, also called a small-sized melanoma, in the scientific literature is commonly defined as a skin melanoma with a diameter of 3 mm or less, although definitions of 5 mm or less can also be found.

Objectives: The aim of this study was to identify the clinical and dermatoscopic features that characterize skin micromelanomas.

Materials and Methods: The study was carried out by searching relevant articles using keyword "micromelanoma" in the following electronic databases – PubMed, Wiley, Scopus, Web of science, ScienceDirect, EBSCOhost, and Google Scholar. The search was performed in the period from January 20th, 2022, to January 31st, 2022. The search had a limit of English language.

Results: According to the published literature, micromelanomas are most often diagnosed in women, since in reviewed studies 43 – 81.8% of patients were women. People diagnosed with micromelanoma are mostly in the age group of 40 to 59 years. Clinically micromelanomas are most frequently seen as dark or light brown macules in diameter of 3 – 4 mm located on the lower extremities and as lesions that had developed *de novo*. The most common diagnostic methods used for micromelanoma diagnostics are physical skin examination and dermatoscopy – polarized light and nonpolarized light. The most widely used diagnostic dermatoscopic algorithm is the 7 – point checklist. Diagnostic accuracy shown for dermatoscopic algorithms is in the range of 48.2 – 65.9%, showing that not all micromelanomas can be diagnosed with diagnostic dermatoscopic algorithms and other characteristics must be considered. The dermatoscopic pattern for micromelanomas is variable – spitzoid, globular, reticular, and structureless, of which spitzoid is the most common. The most common melanoma-specific dermatoscopic signs seen in micromelanomas are irregular dots/globules (25.0 – 88.4% of micromelanomas), atypical network (40.0 – 77.0% of micromelanomas), atypical blotches (16.6 – 38.4% of micromelanomas), and pseudopods (3.4 – 46.0% of micromelanomas). Less frequently other melanoma specific dermatoscopic features – regression, blue – white veil and asymmetric multicomponent dermatoscopic pattern can be observed. Micromelanomas often present asymmetry in structure and color and frequently have two colors dermatoscopically. Micromelanomas rarer than larger melanomas have atypical vessels – dotted, linear, or polymorphous (3.8 – 32.0% of micromelanomas).

Conclusions: Micromelanoma can develop in people of any age and gender, but most commonly it develops after the age of 40 and in women. Micromelanoma develops mainly as a *de novo* lesion on the lower extremities and has a diameter of 1 to 5 mm at the time of presentation. Dermatoscopically, micromelanomas often have melanoma-specific dermatoscopic features, and therefore dermatoscopy aids in diagnosing micromelanoma.

Keywords: Micromelanoma, small-sized melanoma, dermatoscopy, dermatoscopic features, clinical features.

INTRODUCTION

Micromelanoma, also called a small-sized melanoma, is commonly defined in the scientific literature as a skin melanoma with a diameter of 3 mm or less [1-3], although in several scientific publications micromelanoma is defined as a skin melanoma with a diameter of 5 mm or less [4, 5].

Micromelanoma is the earliest clinical manifestation of a melanocytic malignant melanoma [6]. Based on data from the latest literature, approximately 5% of skin melanomas are up to 6 mm in diameter and in recent years there has been an increase in the incidence of such small skin melanomas [1], although in earlier scientific publications reported frequency of

micromelanomas differs, being 11.4 – 38.2% [7]. For melanomas larger than 5 mm it is known that in Europe the incidence rate is 10-25 new melanoma cases per 100,000 inhabitants; in the United States of America 20-30 per 100,000; and in Australia 50-60 per 100,000 [8]. Increase of micromelanoma diagnostics can be explained with several factors, such as, hopefully, patient education and more frequent visits to the dermatologist for prophylactic measures and in cases of new skin formations. Or else, micromelanoma diagnostics have been facilitated by dermatoscopy because it renders magnification and removes surface reflection, thus visualizing structures unseen with the naked eye, besides its use has increased significantly in recent decades.

In scientific literature identified risk factors for micromelanoma are melanoma in patients' history [6, 9-12] or patients' family history [3, 10, 12], patient with

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a dysplastic naevus syndrome [10, 12], the female gender [3, 4, 6, 9, 10, 12-16], age of 40 – 59 years [3-5, 10-15] and II skin phototype by Fitzpatrick [5, 10, 16].

Pathophysiology of micromelanoma is the same as for larger melanomas. It can be explained through aspect of melanocyte, it's unique feature is the production of melanin and in turn, melanin has a complex of antioxidant and prooxidant properties. Its conversion from an antioxidant to a prooxidant agent under the influence of various etiological factors such as UV radiation, heavy metals, herbicides, etc., is the critical and earliest pathogenetic event that initiates carcinogenesis. The prooxidant action of the melanin results in an increase in the levels of intracellular oxygen radicals, which in turn causes damage to the DNA molecule of the melanocyte. The result of these mutations in BRAF, RAS, c-KIT proteins, and others, is excessive activation of various cell signaling pathways, for instance mitogen-activated protein kinase (MAPK) pathway, and results in the uncontrolled proliferation, differentiation, and immortalization of specific cell types [17].

There are several classifications used for melanoma, who can also be used for micromelanoma, one of them is the latest World health organization (WHO) 2018 classification of skin tumors in whom melanoma is classified based on the likely pathogenesis and the degree of its association with sun-exposure [17]. For melanomas arising on sun-exposed skin, classification is based on the degree of cumulative sun damage (CSD) as assessed by the degree of solar elastosis on biopsy specimen – classified as low-CSD melanomas and high-CSD melanomas. WHO classification also includes melanomas arising on non-sun exposed areas [8, 17].

Probably the most used classification system for melanoma, which can also be used for micromelanoma staging, is the newest 8th TNM (Tumor, Node, Metastases) staging system in whom staging is based on the thickness of the lesion and evaluation of its spread to lymph nodes and different tissues in the body, it is also used for clinical staging per the American Joint Committee on Cancer (AJCC). When evaluating melanoma, as well micromelanoma, for staging several important factors, who are also histological prognostic factors, are taken into account – vertical tumor thickness (Breslow's depth), presence of histologically defined ulceration and level of invasion (Clark's level) [18].

As it is known, there are different subtypes of melanoma: cutaneous melanoma is classified as melanoma in situ when confined within the epidermis, or invasive when atypical melanocytes progressively invade into the dermis. As for micromelanomas they can present as in situ or an invasive lesion [4, 5, 7, 9-16, 19, 20]. Subtypes of invasive melanoma have been traditionally distinguished into four major clinic-pathological subtypes: superficial spreading melanoma (SSM) (41%), nodular melanoma (NM) (16%), lentigo maligna melanoma (LMM) (2.7%–14%) and acral lentiginous melanoma (ALM) (1%–5% in non-Hispanic White population and higher rates in Asian or African American population) [8], who are also relevant for micromelanomas, as in several scientific publications [7, 9, 10, 12, 13, 19] there have been diagnosed invasive micromelanomas with a subtype of SSM [7, 10, 12, 13], LMM [9, 10, 12, 19], NM [12].

In micromelanoma diagnostics most commonly used diagnostic methods are visual skin examination [8, 9, 11, 14], dermatoscopy [4-6, 8-15, 19] and total body photography [20] with further surgical excision and histopathological examination [8]. Classical cytological characteristics of melanoma cells seen in histopathological examination include significant cell pleomorphism with a mixture of round, polygonal, spindled, and multinucleated giant tumor cells, melanin pigment in the tumor cells, the presence of eccentric nuclei, prominent nucleoli, and intranuclear inclusions [21]. For melanoma diagnostics also molecular analysis to identify mutations in proteins, such as BRAF, NRAS, c-KIT, NF1, and others is needed. Depending on the staging, additional diagnostic methods can be used [8].

The prognosis of skin melanoma depends mainly on early diagnosis and effective radical treatment before the cancer had spread to other parts of the body. The ability to diagnose skin melanoma in the micromelanoma stage can potentially decrease patient mortality from this cancer [14].

MATERIALS AND METHODS

The study was carried out by searching relevant articles using the keyword “micromelanoma” in the following electronic databases: PubMed, Wiley, Scopus, Web of Science, ScienceDirect, EBSCOhost, and Google Scholar. The search was carried out in the period from January 20th, 2022, to January 31st, 2022.

The following inclusion criteria were defined:

- In a research paper or case report the definition of micromelanoma was fulfilled: the diagnosed micromelanomas were in diameter of 5 mm or smaller.
- For micromelanoma diagnostics, at least one of the following diagnostic methods was used: physical skin examination; dermatoscopy; digital dermatoscopy.
- In a research paper or case report, clinical and dermatoscopic signs of micromelanomas were described.

The following exclusion criteria were defined:

- Duplicates of a research paper or case report in electronic databases.
- The publication was not written in English.

For the research paper or case report to be included in this study, it had to match all inclusion and exclusion criteria.

RESULTS

In total 24 research papers and 3 case reports were found, of whom 3 case reports [9, 14, 16] and 11 research papers [3-6, 10-13, 15, 19, 20] that matched the defined inclusion and exclusion criteria of the authors were reviewed.

Diagnostics of Micromelanoma

From the reviewed research papers, many used physical examination [9, 11, 14, 16], and dermatoscopy [4-6, 9-16, 19] as the main diagnostic methods. The most used diagnostic dermatoscopic algorithm was the 7-point checklist. The diagnostic accuracy of the dermatoscopic algorithms was in the range of 48.2 – 65.9% [10, 12].

In the literature the dermatoscopy was the most commonly used diagnostic method [5, 6, 9-16, 19], which included polarized light [4, 9, 12, 13, 16] and nonpolarized light dermatoscopy [4, 6, 11-14], digital dermatoscopy with polarized light – Fotofinder HD 800 [6], Medicam 1000 [10], Mole Max [10, 13] and total body photography [20]. The diagnostic dermatoscopic algorithms used in the reviewed studies and cases were Chaos and clues [16], TADA (Triage Amalgamated Dermatoscopic Algorithm) [10], 7-point checklist of dermatoscopy [3, 10-12], 3-point checklist of dermatoscopy [12], Menzies method [11, 12], ABCD

algorithm [3, 15] and its total dermatoscopy score [3, 13], and revised pattern analysis [12].

Clinical Signs of Micromelanoma

Micromelanomas are more commonly diagnosed in women [3, 4, 6, 9, 10, 12-16], as 43 – 81.8% of patients were women. Patients mostly are in the age group of 40 – 59 years [3-5, 10-15]. In the research papers micromelanomas were most commonly diagnosed in the age group of 40 – 59 years [3-5, 10-13, 15]. In clinical cases micromelanomas were diagnosed in the interval of 45 – 74 years [9, 14, 16].

The diameter of the diagnosed micromelanomas was in the interval of 1 – 5 mm [3-6, 10-15, 19, 20] (mean 3 – 4 mm) [3, 4, 6, 12-14, 16]. Clinically, micromelanomas have a variable color, with dark brown [6, 10, 22] and light brown [9, 10, 16] being the most common, while black is less common [3, 9]. Most micromelanomas are present as macules [6, 9, 12, 16, 19], rarer as papules [6] or nodules [12]. Among the published studies, the most common location for micromelanomas is on the lower extremities [3-5, 10, 12-15]. Quite often micromelanomas are located on the trunk making it the second most common location [3-6, 10, 12, 19]. Other rarer localizations are upper extremities [4, 6, 10-12, 19], head/neck [4, 6, 10, 12] and face [9, 14, 19] (Table 1).

Some patients with micromelanoma had several risk factors for developing melanoma: melanoma in patients' history [3, 6, 9, 10, 12], melanoma in the family history [3, 6, 10, 12], dysplastic nevus syndrome [10, 12], Fitzpatrick II skin phototype [5, 10, 16]. In several publications micromelanomas developed primarily *de novo* and not from pre-existing nevi [3, 12, 13].

Dermatoscopic Features of Micromelanoma

Dermatoscopic patterns for micromelanomas vary greatly. In the literature there are micromelanomas with spitzoid [3, 5, 10, 12, 14], globular [5, 12], reticular, and structureless [5] dermatoscopic patterns, from which, spitzoid is the most common. Usually, spitzoid dermatoscopic pattern means that it has a starburst or globular pattern of pigmentation that later can evolve to a homogeneous or structureless dermatoscopic pattern [22]. At the same time in one of the included papers (by Slowinska *et al.*) the spitzoid pattern was defined as a starburst pattern with pseudopods or radial streaming or as homogenous pattern with tiered globules, or as

Table 1: Percentage of Micromelanomas Diagnosed on the Head/Neck, Face, and Upper Extremities in the Research Papers

| Author of the research paper, year | Micromelanoma localization on the body | | | | |
|---|--|-------|-------|-------------------|-------------------|
| | Head/neck | Face | Trunk | Upper extremities | Lower extremities |
| Slowinska <i>et al.</i> , 2021 [10] | 2.0% | - | 40.0% | 20.0% | 38.0% |
| Bono <i>et al.</i> , 2004 [6] | 4.6% | - | 22.7% | 72.7% | - |
| Regio Pereira <i>et al.</i> , 2022 [12] | 5.0% | - | 26.0% | 28.0% | 50.0% |
| Vargas-Mora <i>et al.</i> , 2020 [4] | 25.0% | - | 20.0% | 10.0% | 45.0% |
| Megarisi <i>et al.</i> , 2020 [5] | - | 15.4% | 30.7% | - | 38.4% |
| Goldsmith <i>et al.</i> , 2007 [19] | - | 15.4% | 53.8% | 30.8% | - |
| Seidenari <i>et al.</i> , 2014 [11] | - | - | 32.0% | 14.0% | 54.0% |
| Capusan <i>et al.</i> , 2018 [15] | - | - | - | - | 31.1% |
| Otero <i>et al.</i> , 2021 [13] | - | - | - | - | 50.0% |

reticular, globular, atypical, or homogenous pink with multiple dotted vessels [10].

The most common melanoma – specific dermatoscopic signs seen in micromelanomas are irregular dots/globules (25.0 [4] – 88.4% [5] of micromelanomas) [3-5, 10, 12, 13], atypical network (40.0 [10] – 77.0% [3] of micromelanomas) [3-5, 10, 12, 13], atypical blotches (16.6 [4] – 38.4% [5] of micromelanomas) [4, 5, 10], and pseudopods (3.4 [12] – 46.0% [10] of micromelanomas) [5, 10, 12].

Less frequently other melanoma-specific dermatoscopic features are observed – signs of regression [3, 5, 12, 13, 19], blue – white veil [3, 5, 13], streaks – radial [12], peripheral [13], irregular [3, 12] and asymmetric multicomponent dermatoscopic pattern [3, 10]. Other dermatoscopic features seen in micromelanomas are blue – grey dots [10, 12], monocomponent dermatoscopic pattern [3], asymmetry in structure [3, 10, 12, 14] and color [10, 16]. Not all micromelanomas have a melanoma-specific dermatoscopic pattern – in the research paper by Slowinska *et al.* there were 40% of micromelanomas that did not have any melanoma-specific pattern, meaning that micromelanoma corresponded to none of the following: had asymmetric multicomponent pattern, was structureless brown, was a structureless blue-black nodule, or was a structureless pink/tan macule [10]. Macroscopically [3, 6, 9, 10, 16, 19] and dermatoscopically [3, 6, 10, 12] micromelanomas are frequently seen with two colors. As the size of micromelanomas increases, the asymmetry in structure and color, and the number of colors seen dermatoscopically also increases [3]. Important to note – micromelanomas less often (3.8 [5] – 32.0% [10] of

micromelanomas) have atypical vessels – dotted [10, 12], linear [12], or polymorphic [10], which are more characteristic for invasive tumors.

DISCUSSION

Melanoma is a common skin cancer and nowadays with advanced technology and more knowledge it can be diagnosed in more earlier stages and with a smaller diameter than many years before. Based on data from the latest literature, approximately 5% of skin melanomas are up to 6 mm in diameter and in recent years there has been an increase in the incidence of such small skin melanomas [1], showing that micromelanomas are being diagnosed more often. Knowing clinical and dermatoscopic features of micromelanoma can help in diagnostic process.

From the reviewed research papers, most commonly used diagnostic methods were physical examination [9, 11, 14, 16] and dermatoscopy [4-6, 9-16, 19]. In this literature review it was shown that dermatoscopy aided in diagnosing micromelanomas as it was the most commonly used diagnostic method [5, 6, 9-16, 19]. The diagnostic accuracy for dermatoscopic algorithms used in reviewed case reports and research papers was in the range of 48.2 – 65.9% [10, 12], showing that other features in diagnosing micromelanomas need to be considered, such as patients' risk factors for developing micromelanoma and the need for further investigation of the skin lesion using histopathology.

The identified risk factors in this literature review for micromelanoma development such as melanoma in patients' history [3, 6, 9, 10, 12], melanoma in the

family history [3, 6, 10, 12], dysplastic nevus syndrome [10, 12], II skin phototype by Fitzpatrick [5, 10, 16], female gender [3, 4, 6, 9, 10, 12-16], and the age of 40 – 59 years [3-5, 10-15] matched the risk factors in scientific literature for larger melanomas, although the average age of the person diagnosed with larger melanoma is 65 years old [23].

In several publications micromelanomas developed primarily *de novo* and not from pre-existing nevi [3, 12, 13]. As in Otero *et al.* research paper most of the melanomas were not associated with pre-existing nevus and were located on the lower limbs, as the authors state it is probably because there is a higher proportion of *de novo* lesions in this location in comparison with the trunk [13]. For micromelanomas appearing more common as a *de novo* lesions than from pre-existing nevus, it is important to emphasize the need to investigate smaller skin lesions with dermatoscopy in prophylactic visits to dermatologist or the need to use total body photography in patients with risk factors for micromelanoma.

Micromelanomas had variable clinical features – color varied from light brown [9, 10, 16] to black [3, 9], meaning that micromelanomas can be less notable with a naked eye. Micromelanomas more commonly presented as macules [6, 9, 12, 16, 19], rarer as papules [6] or nodules [12], meaning that not always they were in situ lesions. In reviewed research papers invasive micromelanomas were detected in several research papers – Vargas-Mora *et al.* [4], Megaris *et al.* [5], Slowinska *et al.* [10], Seidenari *et al.* [11], Regio Pereira *et al.* [12], and others with a frequency ranging from 25% [20]– 88% [10] [4, 5, 10-13, 15, 19, 20]. And as shown in this literature review micromelanomas have been diagnosed on many sites of the body, but the most common location was the lower extremities [3-5, 10, 12-15], matching the data in literature, as melanomas are more commonly diagnosed on lower extremities in women [24], as in this literature review micromelanomas were more commonly diagnosed in woman and also on lower extremities.

In reviewed literature dermatoscopic patterns for micromelanomas varied greatly – there were micromelanomas with spitzoid [3, 5, 10, 12, 14], globular [5, 12], reticular, and structureless [5] dermatoscopic patterns, from which, spitzoid was the most common. In Slowinska *et al.* research paper authors state that one of the spitzoid patterns might be the first dermatoscopic symptom of micromelanoma

[10]. Different dermatoscopic patterns seen in micromelanomas make their diagnostic process more complex and emphasizes the need to search for melanoma-specific dermatoscopic features or combination of most commonly seen dermatoscopic features of micromelanoma in the skin lesion to diagnose these small sized melanomas. The most common melanoma – specific dermatoscopic signs seen in micromelanomas were irregular dots/globules (25.0 [4] – 88.4% [5] of micromelanomas) [3-5, 10, 12, 13], atypical network (40.0 [10] – 77.0% [3] of micromelanomas) [3-5, 10, 12, 13], atypical blotches (16.6 [4] – 38.4% [5] of micromelanomas) [4, 5, 10], and pseudopods (3.4 [12] – 46.0% [10] of micromelanomas) [5, 10, 12], less frequently other melanoma-specific dermatoscopic features were observed. These percentages for melanoma – specific features show that only several dermatoscopic features are seen in more than 50% of cases making micromelanomas difficult to diagnose using only dermatoscopy.

Macroscopically [3, 6, 9, 10, 16, 19] and dermatoscopically [3, 6, 10, 12] micromelanomas were frequently seen with two colors. Bono *et al.* revealed that as the size of micromelanomas increased, the asymmetry in structure and color, and the number of colors seen dermatoscopically also increased [3], making this a notable finding.

Important to note – micromelanomas less often (3.8 [5] – 32.0% [10] of micromelanomas) had atypical vessels – dotted [10, 12], linear [12], or polymorphic [10] than larger melanomas.

Micromelanoma diagnostics is complex and takes great knowledge and practice as the dermatoscopic pattern and features vary greatly for these small melanomas, thus the dermatologist needs to keep in mind many possible dermatoscopic features that micromelanoma can exhibit.

CONCLUSIONS

Micromelanoma can develop in people of any age and gender, but most commonly it develops after the age of 40 and in women. Micromelanoma develops mainly as a *de novo* lesion on the lower extremities and has a diameter of 1 to 5 mm at the time of presentation. Dermatoscopically, micromelanomas often have melanoma-specific dermatoscopic features, and therefore dermatoscopy aids in diagnosing micromelanoma.

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