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Melanoma – Clinical, Dermatoscopical, and Histopathological Morphological Characteristics

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SUMMARY Melanoma is one of the most malignant skin tumors with constantly rising incidence worldwide, especially in fair-skinned populations. Melanoma is usually diagnosed at the average age 50, but, nowdays is also diagnosed more frequently in younger adults, and very rarely in childhood. There is no unique or specific clinical presentation of a melanoma. The clinical presentation of melanomas varies depending on the anatomic localization and the type of growth, i.e., the histopathological type of the cancer. There are four major histopathological types of melanoma – superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. Although dermatoscopy is a very useful tool in early melanoma detection, dermatoscopical features of melanomas are also variable. Therefore, experience and education in dermatoscopy is crucial in the evaluation of skin tumors. Differential diagnosis of melanomas includes a wide range of benign and malignant skin lesions, due to their clinical presentation and resemblance to various dermatological entities. In this review we present the most important aspects of clinical, dermatoscopical, and histopathological features of melanomas.

KEY WORDS: melanoma, clinical characteristics, histopathological characteristics, dermatoscopy

INTRODUCTION

Melanoma is a malignant tumor which evolves from melanocytes and is one of the most aggressive malignant tumors of the skin and mucosa. It is characterized by a high tendency of early lymphatic and hematogenous spreading accompanied with lower local aggressiveness. During the last four decades, a continuous increase in the incidence of melanoma (from 3 to 8% per year) has been registered worldwide, with the highest incidence in Australia, where melanoma is the fourth most frequent malignant tumor (1). In Western European countries, the survival of patients with melanoma has been prolonged in recent years, which can be explained by melanoma detection at an earlier stage. The incidence and mortality rates of melanoma in Croatia have been increasing by 140% and 50% respectively during the last two decades, which is in accordance with world trends (2,3). Melanoma represents approximately 3% of all malignancies in Croatia. According to the latest available data from the Croatian National Cancer

Registry, there were 555 newly diagnosed melanoma patients in 2010 (260 women and 295 men). The melanoma incidence rate in Croatia was 12.6/100000 (11.4/100000 for women and 13.8/100000 for men) in 2010 (4), whereas the mortality rate of melanoma was 0.39/100000 (0.37/100000 for women and 0.40/100000 for men) (5).

In the epidemiological study from the Croatian Referral Centre for Melanoma which included more than 700 melanoma patients, the mean tumor thickness at the time of diagnosis was 2.24 mm (6). Melanomas usually occur on skin intermittently exposed to the sun, with predilection for shoulders and back in men and lower extremities in women. Melanoma is usually diagnosed at the average age of 50. However, during recent decades, melanoma is more often diagnosed in young adults at the age of 25-40, and sometimes, though rarely, in childhood. The etiology of melanoma includes intrinsic risk factors (family history of melanoma, previous melanoma or non-melanoma skin cancer, type and number of nevi, skin type, and immunosuppression) and environmental factors, most importantly UV radiation (7,8).

Clinical, dermatoscopical, and histopathological morphological characteristics of melanoma

There is no typical clinical presentation of melanoma. The major clinical finding is a pigmented skin lesion, showing clinically important changes over a period of time (months or years). Every skin lesion changing in color, shape, or size, with irregular borders, or associated with a burning feeling, itching or pain, should be closely evaluated. The above mentioned changes are part of the "ABCDEFG rule" which is very important in clinical examination of every pigment lesion (A– asymmetry, B– border, C– color, D– diameter, E– elevation or evolution, F– feeling, G– growth). The clinical presentation of melanoma varies depending on the anatomic localization and the type of tumor growth, namely the histopathological type. There are four major histopathological types of melanoma – superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM).

In everyday practice, the "ugly duckling sign" is a very useful clinical diagnostic tool for detecting suspicious lesions. This method is based on the observation that each person with multiple nevi has a relatively specific "profile" of nevi (morphologically predominant type of nevi in an individual). Therefore, a lesion that looks different than other surrounding lesions should be considered suspicious (the "ugly duckling") and more closely examined or excised.

In melanomas, both clinical presentation and dermatoscopical features are extremely variable. Melanomas have dermatoscopical features indicating their melanocytic origin, such as pigment (melanocytic) network, aggregated brown or black globules, and site-specific features (e.g. parallel patterns on palms and soles, follicular openings on facial skin, etc.) (9). However, in some cases, a melanoma may be clinically and dermatoscopically relatively featureless, and in such cases even experienced dermatologists may have difficulty recognizing the melanoma.

The 3-point checklist is a dermatoscopical algorithm developed as a screening method to prevent those with little training from misdiagnosing melanoma and to improve their skills. The following three criteria are especially important in distinguishing a melanoma from other pigmented skin lesions: dermatoscopical (not necessarily clinical) asymmetry in color and structure, atypical pigment networks, and blue-white structures (10). It is recommended that all lesions with a positive test (3-point checklist score of 2 or 3) should be excised and histopathologically analyzed. There are several other dermatoscopical algorithms which may be helpful in the evaluation of skin lesions, including pattern analysis, the ABCD rule, the Menzies method, the Seven-point checklist, and the CASH algorithm.

Superficial spreading melanoma (SSM)

SSM is the most common type of melanoma in the Caucasian population, accounting for 70-80% of all melanomas (11). It is usually diagnosed at 30 to 50 years of age, and occurs more often in women. This type of melanoma can arise in any anatomic localization, most frequently on the trunk in men and on lower extremities in women. Patients usually report changes having taken place in the pigmented lesion within the last 1 to 5 years. Initially, in its horizontal growth phase, SSM presents as a light brown to black colored macule, with irregular borders. In the vertical growth phase, the surface is rough or papillomatous and may be ulcerated (Figure 1.).

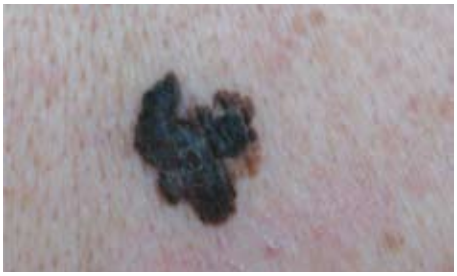

Figure 1. Superficial spreading melanoma on the back of a 58-year-old man, showing a variety of colors, irregular borders, asymmetry, and a partially elevated and rough surface.

Dermatoscopy of an SSM usually shows one or more of the following dermatoscopical features: a blue-white veil (histopathologically corresponding to melanin in the mid-dermis with overlying epidermal orthokeratosis), multiple brown dots (corresponding to suprabasal epidermal malignant melanocytes representing the pagetoid spread of SSM), pseudopods and radial streaming (corresponding to confluent radial nests of atypical melanocytes at the dermoepidermal junction), scar-like depigmentation or white milky areas (areas of tumor regression), peripheral black dots and/or globules (representing malignant melanocytes found at or near the stratum corneum), multiple colors, a broad and atypical network (rete ridges filled with malignant melanocytes), focal sharply cut-off borders, crystalline structures or chrysalis (which can be observed with polarized dermatoscopy only, corresponding to an altered stromal matrix), and irregular vascular structures (12) (Figure 2).

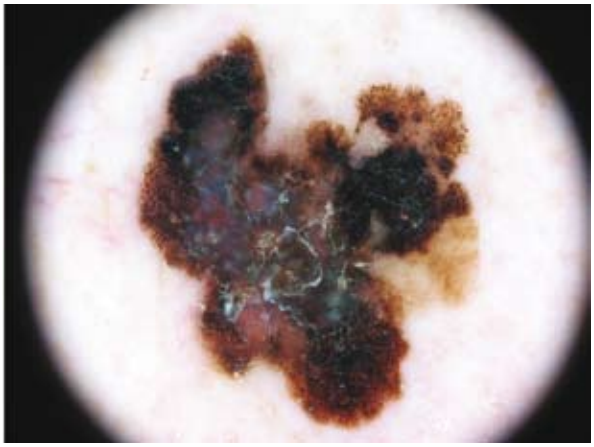

Figure 2. Dermatoscopical presentation of SSM; absolute asymmetry in shape and color, a broad and atypical network, focal sharply cut-off borders, multiple colors, a blue-white veil, and crystalline structures.

The histopathological features of SSM include asymmetry, poor circumscription (13,14), and lack of cellular maturation. Malignant melanocytes spread throughout the layers of the epidermis as single cells and nests (the horizontal growth phase). The intraepidermal component extends laterally for more than three rete ridges beyond the dermal component (15). The vertical growth phase is characterized by mitoses or nests of malignant melanocytes in the dermis, often accompanied by a lymphocytic infiltrate (16). The melanocytes are epithelioid, with large nuclei and abundant cytoplasm (Figure 3).

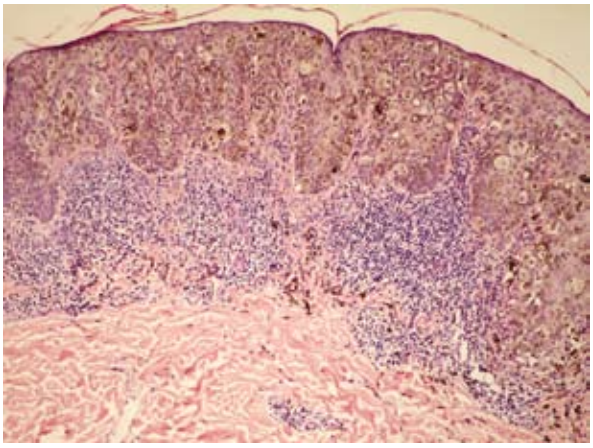

Figure 3. Histopathological features of superficial spreading melanoma; large atypical melanocytes with nest formation along the dermo-epidermal junction, and invasion of the upper epidermis in a pagetoid fashion (H&E; x100).

Nodular melanoma (NM)

Nodular melanoma is the second most common type of melanoma, accounting for 15–30 % of all melanomas (17). It is usually diagnosed in people between 40 and 50 years of age, equally frequent in both sexes. The most common localizations are the trunk, head and neck. Evolution of the lesion is usually brief – the lesion develops in just a few months to 2 years prior to diagnosis. This type of melanoma is considered to be more aggressive than the SSM and often develops rapidly. It is usually darker than the SSM, is well circumscribed, and presents as a uniformly colored nodule with or without ulceration. NM often features distinct pigmentation and a glossy surface, which enables clinical recognition of this type of melanoma (Figure 4). Due to a very brief horizontal growth phase and early onset of the vertical growth phase, NM is usually diagnosed at an advanced stage (16). Even very small lesions of NM have metastatic potential.

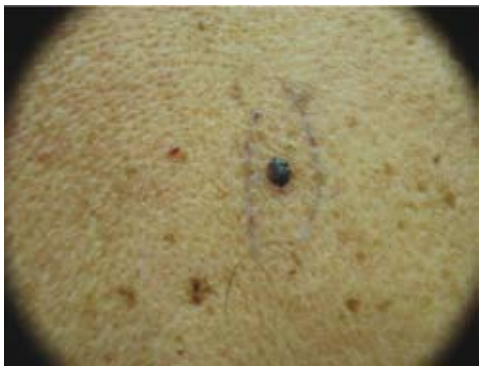

Figure 4. Nodular melanoma on the back of a 50-year-old man; the lesion developed within 8 months.

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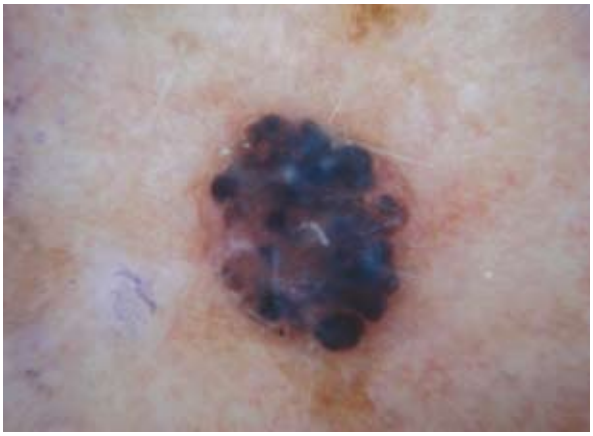


Figure 5. Dermatoscopy of nodular melanoma, showing asymmetrically distributed dark globules, multiple colors, and a blue-white veil.

Dermatoscopical features of NM include: isolated globules, a blue-white veil, white streaks, and irregular linear or dotted vessels (Figure 5.). One of the recently described dermatoscopical features which can help in detecting pigmented NM is the presence of a combination of blue and black color within the lesion (the „blue-black rule“) (18).

Features like networks, streaks, and regression structures are not seen in NM. Moreover, NM can also be missed by dermatoscopy if the features of the melanoma are not noted at the periphery of the lesion, or if the lesion is amelanotic. In amelanotic NM, dermatoscopical clues such as atypical vessels or crystalline structures (19) may be helpful in the diagnosis.

Histologically, an epidermal component is limited to less than three rete ridges in width. The dermal component is characterized by a nodular confluence of atypical melanocytes. The neoplastic cells are epithelioid or spindled, with frequent and often atypical mitoses (14) (Figure 6).

Polypoid melanoma

Polypoid melanoma is an aggressive subtype of nodular melanoma, although polypoid configuration can be present in other histological types of melanoma. Compared to nodular melanoma, polypoid melanoma is characterized by increased thickness, more frequent ulceration (20,21), younger age at diagnosis, and higher risk for occult metastases. Histologically, it is characterized by an aggregation of a large volume of melanoma cells above the surface of the skin (22). Usually, it is localized on the trunk, although it can occur on mucosal surfaces, including the upper respiratory tract, esophagus, vagina, and rectum (21).

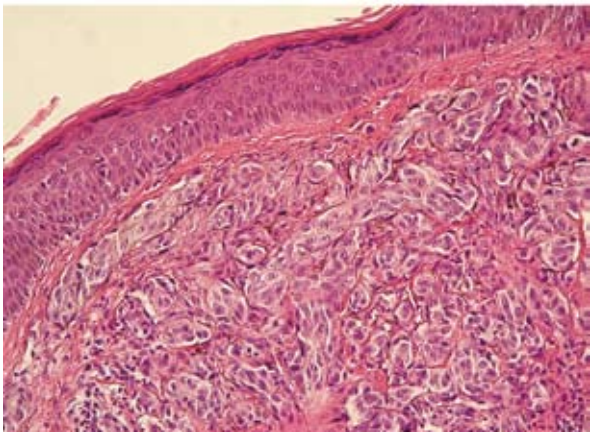


Figure 6. Histopathological features of nodular melanoma; thin epidermis, a dermal nodule of melanocytes with a “pushing” growth pattern, no “radial growth phase”(H&E; x100)

Lentigo maligna melanoma (LMM)

Between 5% and 15% of all melanomas are diagnosed as LMM (17), usually in patients older than 65 years, equally in both genders. LMM most commonly develops on chronically sun-damaged skin, especially on the nose and cheeks, which suggests that the cumulative effect of UV radiation is crucial in the development of this type of melanoma. The precursor skin lesion of invasive LMM is lentigo maligna (LM), which is histopathologically defined as LMM *in situ*. LM presents as a macule of various shapes with irregular brown pigmentation, 3-6 cm in size, usually poorly circumscribed, slowly growing for years (even up to 30 years) (Figure 7.). LM undergoes a horizontal growth phase for 15 years or more, prior to transforming into invasive LMM. The occurrence of dark areas/nodules and/or infiltration in LM indicates progression into LMM (Figure 8). According to the

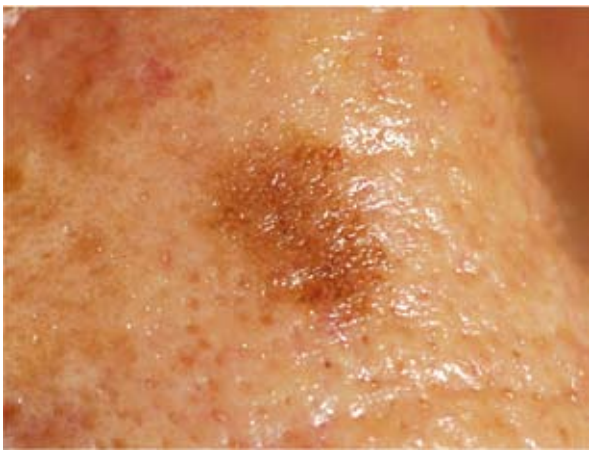


Figure 7. Lentigo maligna on the nose, clinical presentation.

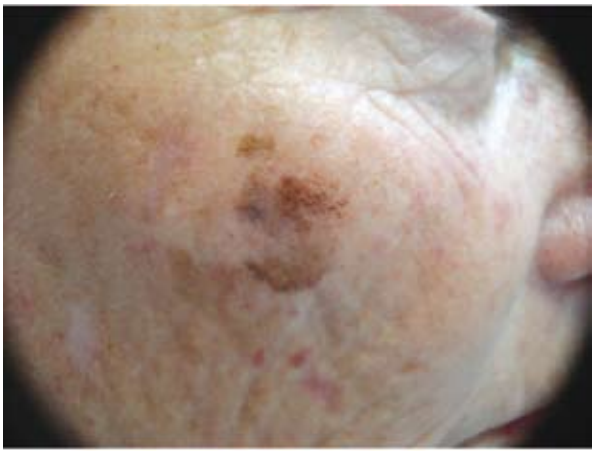


Figure 8. Lentigo maligna melanoma on the cheek of a 70 year-old woman.

literature, the progression rate of LM into LMM varies from 5% to 50% (23,24). Major dermatoscopical features of LMM are: asymmetrically pigmented follicular openings (reflecting a non-uniform infiltration of atypical melanocytes along the circumference of the follicular epithelium), dots and globules aggregated around adnexal openings (brown dots reflecting melanocytes and small nests at the dermoepidermal junction, and blue-gray granularity reflecting melanophages in the dermis), annular-granular pattern (dots aggregated around adnexal openings or short polygonal lines around and between adnexal openings), and thick pigmented lines surrounding follicular openings, sometimes called rhomboidal structures (representing more extensive infiltration of the dermoepidermal junction by confluent nests and aggregates of melanocytes) (Figure 9). Invasive LMM may also present other previously described features typical of invasive melanoma (25).

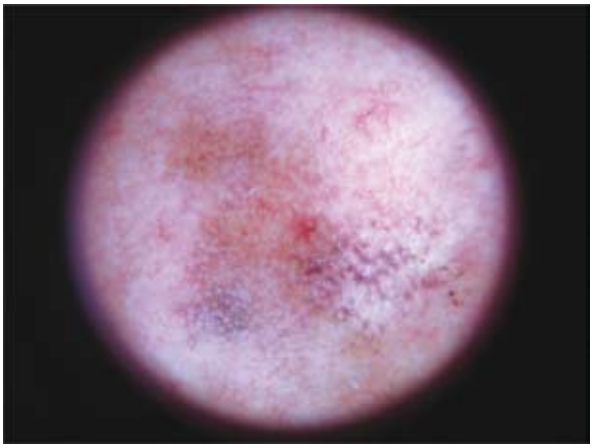


Figure 9. Dermatoscopical features of lentigo maligna melanoma; asymmetrically pigmented follicular openings as well as dots and globules aggregated around adnexal openings.

The histopathological characteristic of LMM is lentiginous proliferation of atypical melanocytes in the epidermal basal layer. The epidermis is atrophic, and atypical melanocytes are polygonal with atypical nuclei (14). The vertical growth phase is characterized by formation of nodules in the dermis with marked solar elastosis. Atypical melanocytes show lentiginous proliferation down the adnexal structures (Figure 10). Lymphocytic infiltrate admixed with plasma cells and melanophages is a commonly found in the upper dermis.

Acral lentiginous melanoma (ALM)

Among the four major histopathological types of melanoma, ALM is the least common type, accounting for 2-8% of all melanomas in Caucasians. However, this is the most common type of melanoma diagnosed among Asians and dark-skinned individuals. It affects the glabrous skin, with a predilection for palms, soles and subungual areas. It usually occurs in the sixth or seventh life decade, more commonly in men. ALM develops in several months or up to several years. Initially, it presents as an unevenly brown pigmented macule with irregular borders (26). The lesion can reach the size of up to 3 cm, with possible formation of a nodular component. Subungual location is a common location of ALM, especially on the big toe. It presents as a longitudinal brown or black nail band, sometimes accompanied by nail distrophy. When Hutchinson's sign is present (pigmentation of the nail fold and surrounding skin), the clinical diagnosis is almost certain. Sometimes, ALM may present with a verrucous surface, which is why this tumor sometimes remains unrecognized for a long time and is occasionally even mistreated with destructive

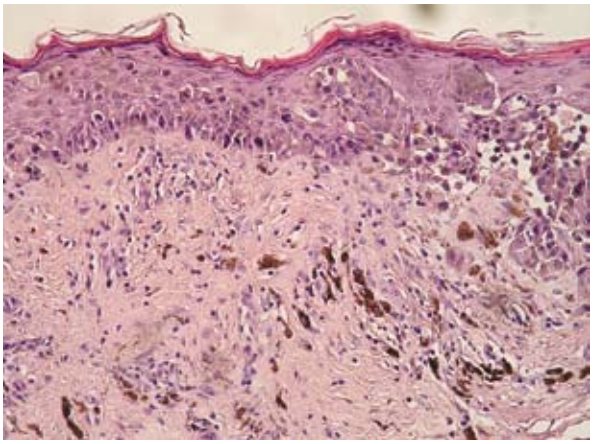


Figure 10. Histopathological features of lentigo maligna melanoma; single, hyperchromatic melanocytes along the basal and suprabasal layer of the epidermis surrounded by a clear space (H&E; x100)

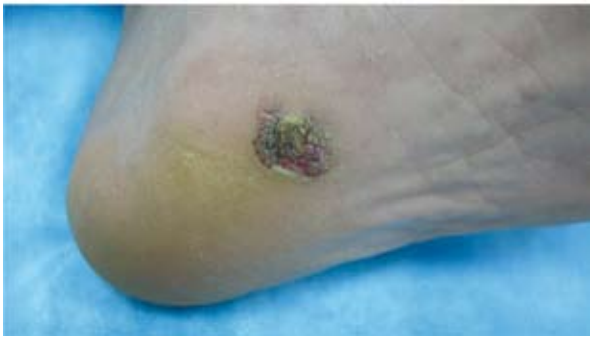


Figure 11. Acral lentiginous melanoma on the foot. This tumor was present for two years and was unsuccessfully treated (in another institution) as a wart, using a topical keratolytic agent and cryotherapy. Finally, the lesion was biopsied and the diagnosis of ALM was confirmed. Sentinel lymph node biopsy was also performed and was positive.

methods resulting in delayed diagnosis only at an advanced stage (Figure 11).

Dermatoscopically, ALM is characterized by a broad parallel ridge pattern (in contrast to the benign parallel furrow pattern in acral nevi). The dermatoscopical features of SSM described previously may be present, especially irregular diffuse pigmentation and a multicomponent pattern (27).

Histologically, ALM is characterized by confluent single-cell melanocytic proliferation along the dermo-epidermal junction. Atypical melanocytes are usually spindle-shaped. As the tumor progresses, large junction nests composed of atypical melanocytes are seen, as well as a pagetoid spread (Figure 12).

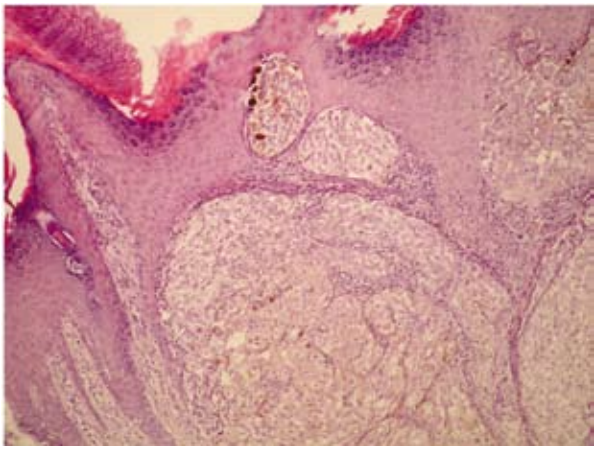


Figure 12. Histopathological features of acral lentiginous melanoma; irregular epidermal hyperplasia, melanocytic cells with nest formation along the dermo-epidermal junction and in the dermis (H&E; x100)

Unusual variants of melanoma

Other forms of melanoma, such as amelanotic melanoma, desmoplastic melanoma, verrucous melanoma, nevoid melanoma, and metastatic melanoma of unknown primary site, are rarely encountered in clinical practice.

Desmoplastic melanoma (DM)

Desmoplastic melanoma is a rare variant of melanoma that accounts for less than 4% of all primary cutaneous melanomas (28,29). It usually occurs between 60 and 65 years of age (30), more commonly in men. The predilection site is sun-damaged skin of the head and neck where it can be associated with LM, although any localization, including mucosal surfaces, may be involved (31,32). DM is often diagnosed late, due to a frequent amelanotic clinical appearance; it is highly infiltrative with predisposition to perineural spread and local recurrences (31). The most common clinical finding is an amelanotic, pale nodule or plaque that may resemble a scar (33). The histopathological features of DM include a poorly circumscribed, mainly intradermal, ill-defined spindle cell neoplasm in a background of stromal desmoplasia (variably increased collagen fibers) and frequent neurotropism of neoplastic melanocytes. The neoplastic cells are elongated, spindled with scant pale cytoplasm and large elongated and irregular nuclei. DM usually invades the surrounding dermis and subcutaneous tissue. Lentiginous proliferation of atypical melanocytes or even lentigo maligna (34) can be found within the epidermis in up to 50% of all lesions. Focal lympho-

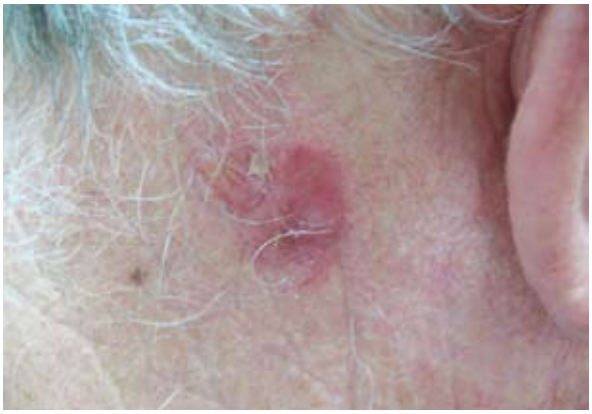
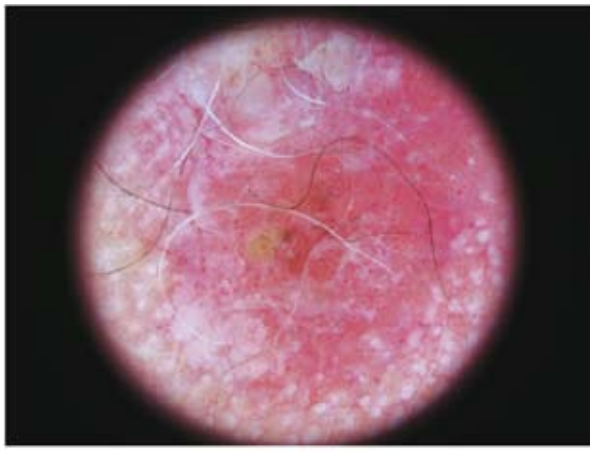


Figure 13. A pink and crusty lesion which developed in the retroauricular area, unsuccessfully treated as an eczema in another institution, using topical steroids for a year. After the excision and confirmed diagnosis of amelanotic melanoma, a sentinel lymph node biopsy was performed and was positive. The patient also had multiple visceral metastases at the time of diagnosis.



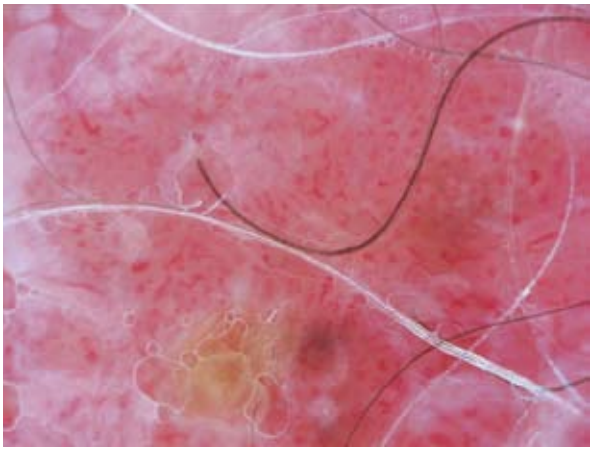


Figure 14 and 15. Dermatoscopical picture of the amelanotic melanoma presented in Figure 13. In this case, polymorphous vascular structures (dotted, glomerular, and corkscrew) were the clues to the diagnosis.

cytic aggregates and mucin can be seen in the dermis. The mitotic index is usually low. Immunohistochemical analysis shows tumor cells positive for S-100 protein. DM can be divided into two subtypes: "pure" and "mixed", i.e. with prominent stromal desmoplasia, or a combination of desmoplastic and nondesmoplastic components, respectively. "Pure" DM shows a significantly lower incidence of lymph node metastasis and a lower 5-year melanoma-specific mortality, in comparison to patients with the "mixed" type of DM (31). DMs which show prominent neural invasion and/or neural differentiation have been termed desmoplastic neurotropic melanomas (35,36).

Nevoid melanoma

Nevoid melanomas comprise a group of melanomas that resemble melanocytic nevi cytomorphologically, but also have histological features and the biologic behavior of melanomas with metastatic potential (37). Nevoid melanomas are rare lesions, accounting for less than 1% of all melanomas. Clinically, nevoid melanomas mimic nevi and usually present as a verrucous or dome-shaped pigmented nodule. The histopathological features of nevoid melanoma include dermal mitoses, a sheet-like growth pattern of neoplastic nevoid cells in the dermis, and cytological atypia. A lack of typical melanoma features, such as asymmetry, poor circumscription, or pagetoid growth of melanocytes, is common. Additionally, unconventional "maturation" of the dermal component may be present (38).

Amelanotic melanoma (AM)

AM is a melanoma with a lack of distinct pigmentation. Each histopathological subtype of melanoma can occur as an amelanotic variant, although it is more common within subungual tumors (25%), desmoplastic melanoma (more than 50%), cutaneous melanoma metastases, and NMs. An amelanotic appearance often results in delayed diagnosis (39). Amelanotic variants of melanoma are rare lesions, accounting for 2% to 8% of all cutaneous melanoma (40,41). AM presents as pink or flesh-colored lesion, often mimicking basal cell, squamous cell carcinoma, or dermatofibroma (Figure 13). One should always be careful when examining a patient reporting a change in an odd-looking pink lesion, especially when there is a history of previous unsuccessfully applied local treatment.

AM can be difficult to diagnose, both clinically and dermatoscopically. In the majority of AMs, there is a small amount of focal irregular pigmentation, often at the periphery of the lesion. In such cases, the crucial dermatoscopical finding for making the correct diagnosis is often an atypical vascularity, such as linear, dotted, corkscrew, or polymorphous vessels. Therefore, it is very important not to apply too much pressure with the dermatoscope during examination, since that may obscure the vascular pattern.

Verrucous melanoma

Verrucous melanoma is a rare variant of melanoma which presents as a nearly uniformly colored hyperkeratotic verrucous lesion, which often resembles seborrheic keratosis (42,43,44). It affects the female gender more often, and can occur at any localization, but more commonly on the extremities (43). Histopatologically, verrucous melanoma is characterized by prominent papillomatous epidermal hyperplasia with varying degrees of hyperkeratosis, parakeratosis, and acanthosis (20). This verrucous configuration is in line with conventional histological types of melanoma according to Clark's classification. One third of the cases do not fit into this classification. The prognosis for verrucous melanoma corresponds to that for non-

verrucous melanomas matched for sex, anatomic site, and thickness of the neoplasm.

Melanoma metastases of unknown primary origin

Melanoma is one of the most aggressive neoplasms, with propensity towards early lymphatic and hematogeneous spread. Melanomas usually metastasize to regional lymph nodes and then to the liver, lungs, bones, or brain via blood vessels. Melanoma also frequently metastasizes to the skin, either in proximity of the primary lesion, or to distant localization as an outcome of hematogeneous spread. Satellites and in-transit metastases are typical for melanoma, developing between the site of the primary tumor and regional lymph nodes (45), in the lymphatics of the skin and subcutaneous tissue. Satellite metastasis is a tumor cluster which is separated from the primary tumor by normal tissue, and is confined within a radius of 2 cm from the primary tumor. In-transit metastases are localized between more than 2 cm from the primary lesion and regional lymph nodes. The incidence of metastatic melanoma (including skin, lymph nodes and viscera) with unknown primary tumor ranges from 2% to 5% (46,47). Occasionally, the melanoma can originate at an extracutaneous site such as the retina, the anal canal, or on mucosal surfaces, and can be followed by complete regression. Regression in melanoma is well documented, with a frequency of up to 10%. Metastatic cutaneous melanoma clinically presents as a bluish intradermal papule or palpable nodule in the subcutaneous tissue.

Histologically, cutaneous metastases are dermal or subcutaneous nodules composed of epitheloid and/or spindle cells without an epidermal connection and without significant inflammatory response (48). Rarely, epidermal involvement can be present, and in such cases, the term epidermotropic metastasis is appropriate (49).

The rare phenomenon of a primary dermal melanoma confined to the dermis and/or subcutaneous tissue and without an epidermal component presents a major diagnostic challenge (50). It is a subtype of melanoma that resembles metastasis histologically, but is associated with an unexpectedly prolonged life expectancy in comparison with cutaneous metastasis (51). Primary dermal melanoma can occur at any localization (51, 52).

Multiple primary melanomas (MPM)

The appearance of multiple primary melanomas (MPM) in the same patient is an uncommon phenomenon, occurring in 0.2% to 8.6% of all cases (53). In an epidemiological study of the Croatian Referral Centre for Melanoma (54), which included 991 registered melanoma patients during a 7-year-period (2002–2008), 36 patients (3.6%) were diagnosed with MPM, most of them (78%) having two primary melanomas, which is in agreement with previous studies (53, 55). The most common histological type of melanoma was SSM. Among secondary melanomas, there less NMs and more LMMs were diagnosed, compared to their incidence as primary melanomas. According to the majority of reported studies, most of the subsequent melanomas are diagnosed within 2 years from the diagnosis of the first melanoma. The highest risk of the secondary melanoma is during the first 5 years (54). Synchronous lesion of MPM (multiple tumors diagnosed within 30 days of each other) occurs in 20–40% of MPM patients (53). Tumor invasion, with reference to Breslow's thickness (56) and Clark's level (57) of subsequently diagnosed melanomas, is significantly decreased compared to the first melanoma. Risk factors for the development of MPM include: a personal history of prior melanoma, positive family history of melanoma (first-degree relatives), and the presence of dysplastic nevi (58). Approximately 6–12% of the melanomas are family cases. Patients with numerous dysplastic nevi and a positive family history of melanoma are at the highest risk. In these patients, melanoma is on average diagnosed 10 years earlier than in the general population. They are also at higher risk of developing MPM.

Table 1. Differential diagnosis of melanoma

Solar lentigo
Senile lentigo
"Caffe au lait" macule
Verrucae vulgares
Seborrheic keratoses
Dysplastic naevus
Blue naevus (*naevus coeruleus*)
Spitz/Reed naevus
Pigmented basal cell carcinoma
Pigmented actinic keratosis
Mb. Bowen
Invasive squamous cell carcinoma
Pigmented adnexal tumors
Vascular tumors
Other tumors (fibroma, dermatofibroma)
Subungual hematoma
Melanonychia striata
Some tattoo forms (eg. amalgam tattoo)
Solitary giant comedo

Differential diagnosis of melanoma

In the literature melanoma is often called "the great imitator" due to its varied clinical presentation and resemblance to different dermatological entities. Differential diagnosis of melanoma includes: solar and senile lentigo, "cafe au lait" macule, *verrucae vulgares*, seborrheic keratoses (especially in cases of very dark or pigmented solitary lesions), atypical nevus, blue nevus (*nevus coeruleus*), Spitz/Reed nevus (fast growing lesions, sometimes with intense dark brown to black pigmentation), pigmented basal cell carcinoma, pigmented actinic keratosis, Bowen's disease (squamous cell carcinoma *in situ*), invasive squamous cell carcinoma, pigmented adnexal tumors, vascular tumors (angiokeratoma, thrombosed hemangioma, pyogenic granuloma, glomus tumor, Kaposi sarcoma, senile hemangioma), other tumors (fibroma, dermatofibroma which can mimic desmoplastic melanoma), subungual haematoma, corneal hemorrhage („black heel"), melanonychia striata, some forms of tatoo (eg. amalgam tattoo of the oral mucosa), and solitary giant comedo (Table 1) (59).

Prognostic factors of melanoma

Several clinical (age, sex, anatomical localization of the tumor) and histopathological findings are reported as important prognostic factors in melanoma patients.

Every histopathological report of a melanoma should therefore contain the following information: histological type of tumor, tumor thickness (Breslow depth), Clark's classification, presence or absence of ulceration, regression, mitotic index, presence and amount of tumor infiltrating lymphocytes (TIL), presence of capillary invasion and microscopic satellites, and presence of perineural invasion (13). The status of

Table 2. TNM Staging Categories for Cutaneous Melanoma, American Joint Committee on Cancer – AJCC, 2010 (60)

Classification		Thickness (mm)	Ulceration status/Mitoses
T			
	Tis	NA	NA
	T1	≤1.00	a: without ulceration and mitosis <1/mm^2
			b: with ulceration or mitoses ≥1/mm^2
	T2	1.01-2.00	a: without ulceration
			b: with ulceration
	T3	2.01-4.00	a: without ulceration
			b: with ulceration
	T4	>4.00	a: without ulceration
			b: with ulceration
N		**No. of metastatic nodes**	**Nodal metastatic burden**
	N0	0	NA
	N1	1	a: micrometastases*
			b: macrometastases†
	N2	2-3	a: micrometastases *
			b: macrometastases †
			c: In-transit metastases/satellites without metastatic nodes
	N3	≥4 metastatic nodes or matted nodes, or in-transit metastases/ satellites with metastatic nodes	
M		**Site**	**Serum LDH**
	M0	no distant metastases	NA
	M1a	distant skin, subcutaneous, or nodal metastases	normal
	M1b	lung metastases	normal
	M1c	all other visceral metastases	normal
		any distant metastasis	elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.

*Micrometastases – diagnosed after sentinel lymph node biopsy.

†Macrometastases – are defined as clinically detectable nodal metastases confirmed pathologically.

local lymphnodes (evaluated by sentinel lymphnode biopsy) also has an important prognostic significance in melanoma patients (13).

The American Joint Committee on Cancer (AJCC) TNM classification of melanoma, dating from 2001, has been revised in 2009 after evaluation of clinical and pathological factors in almost 60,000 melanoma patients. The revised seventh edition of the AJCC Cancer Staging manual is effective as of January 2010. The current AJCC melanoma classification (Table 2) has introduced mitotic rate as an important independent prognostic factor in addition to tumor thickness and ulceration in patients with localized melanoma (60). Recent studies have shown that invasion level according to Clark is a statistically insignificant prognostic factor in comparison to the mitotic index (number of mitoses per mm^2) and presence of ulceration in patients with T1 stage melanoma. Clark level has been recognized as an important prognostic factor only in T1b melanoma patients when there is no possibility to determine a precise mitotic index. Also, according to the current AJCC classification, imunohistochemical detection of isolated tumor cells or tumor deposits < 1mm, with at least one marker such as HMB-45, Melan-A, MART-1, is sufficient for the diagnosis of lymphatic micro metastasis in cases where diagnostic cellular morphology is absent (60).

CONCLUSION

Melanoma is one of the most heterogeneous tumors in terms of clinical, dermatoscopical, and histopathological presentation. Therefore, differential diagnosis of melanoma includes a whole range of benign and malignant skin lesions. For patients with melanoma diagnosed at an advanced stage, treatment options are still modest. However, if a melanoma is recognized and surgically removed at an early stage, it can be considered a curable disease with an excellent prognosis. Therefore, early detection of melanoma remains the most important step in improving patient outcomes.

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