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Review article

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New pathomorphological classification of melanomas

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Melanoma is a neoplasm whose biology we are getting to know better and better. The consequence of this is the latest edition of "WHO Classification of Skin Tumours 4th edition, 2018". The division presented in this paper takes into account the character of growth and location of melanoma, but also results from the analysis of the most frequent mutations occurring in this neoplasm. The assessment of the stage of melanoma progression, based on two most important prognostic microscopic features, i.e. the depth of infiltration and the presence or absence of ulceration, remains valid.

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Melanoma, from a clinical and pathological point of view, makes up a heterogenous disease entity. The basis for the classification of this tumour was worked out by W.H. Clark [1] and V.J. McGovern [2] in the 1970s. The classification which they proposed presents melanoma as a melanocytic lesion, which, within its development, undergoes progression. The first stage is defined as melanoma in situ. This type of melanoma is characterised by the presence of atypical melanocytes:

- melanocytes, located on the entire thickness of the epidermis, are irregularly placed, creating pagetoid-like groups (superficial spreading melanoma in situ); or:
- in the basal layers of epidermis, placed in a linear and lentiginal way (lentigo melanoma in situ).

In the case of melanoma in situ and/ or accompanying melanocyte infiltration in the upper layers of the skin, the prognosis is defined as very good. The phase of melanoma growth is defined as the radial growth phase (RGP). It precedes the melanoma's progression into the skin, a process which consists in transgressing the basal membrane of the epidermis and an infiltration into the lower skin layers with the creation of a nodule. This stage is defined as the vertical growth phase (VGP). It is connected with the progression of a lesion and has a poor prognosis.

The creators of the most recent classification of skin tumours, the "WHO Classification of Skin Tumours 4th edition, 2018" [3] point to two basic types of melanoma: melanomas with the radial phase and those which since their onset begin to develop in a vertical way. The first group comprises: a superficial spreading melanoma and a malignant lentigo. The other group comprises nodular melanoma, which has only a vertical phase and naevoid melanoma, which usually does not have a radial phase.

The above listed melanoma groups differ from one another in terms of their ontogenetic mechanisms, and the genetic changes occurring within them as well as their clinical picture. The main ontogenetic mechanism is the damage caused by the UV radiation connected with exposure to the sun (or artificial UV radiation). High-energy UVB rays, which make up 5% of the radiation which reaches the Earth, penetrate the skin, damaging the epidermis and causing tumours.

The most recent WHO classification proposes the division into the skin melanomas based on the factors which cause the disease:

- significant damage to the skin resulting from a cumulative dose of sun radiation (high cumulative skin damage, high-CSD melanoma);
- and slight damage to the skin caused by a small or sporadic UV exposure (low cumulative skin damage, low-CSD melanoma).

The first group of melanomas contains a large number of punt mutations; in particular the mutations in the following genes are typical: *NF1*, *NRAS*, *BRAF* (other than p. V600E), KIT (MAPK activation pathway), TP53. Melanomas of the skin which have been chronically exposed to sun (high-CSD melanoma/melanocytic tumours in chronically sun-exposed skin) comprise: lentigo malignant melanomas and desmoplastic melanomas. In the low-CSD melanomas, the mutation in the codon 600 *BRAF* gene is dominating (*BRAF* p. V600E). This group is also comprised of the low-CSD melanoma/superficial spreading melanoma.

There is also a group of melanomas that have no connection to UV exposure. These are: acral melanoma, mucosal melanoma, uveal melanomas and Spitz melanomas. In these melanomas, the following gene mutations are detected: *HRAS* (Spitz melanoma), *KIT*, *NRAS*, *BRAF*, *HRAS*, *KRAS*, *ALK*, *NTRK3* (acral melanoma), *KIT*, *NRAS*, *KRAS* (mucosal melanoma) and *GNAQ*, *GNA11*, *CYSLTR2* (uveal melanoma).

Moreover, in all three types of these melanomas, there is a mutation of the CDKN2A gene, coding p16 protein which performs the function of a tumour suppressor within a cell. The loss of p16 expression in the immunohistochemical reaction is a proof of the presence of melanoma, and this is why the quantification of this protein is used in histopathological deferential diagnosis [4, 5]. A detailed list of genetic changes occurring in specific types of melanocyte proliferations is presented in figure 1.

Apart from the above-listed mutations, high-CSD melanomas contain a very high mutation burden, whilst, for example, in acral melanomas and mucosal melanomas the mutation burden is low, and in uveal melanomas – even lower. Amongst many genetic anomalies, the mutations of the *BRAF* V600E and *C-KIT* genes have predictive significance – and for this reason the tissue material containing the cell pattern of the primary or metastatic melanoma is assessed with regards to the presence of these mutations.

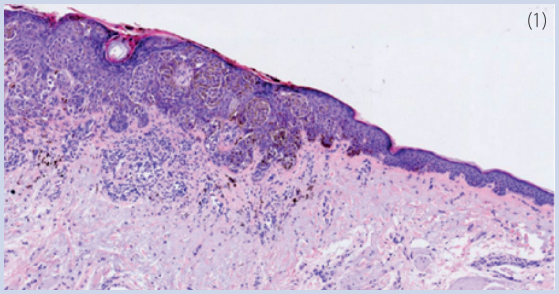
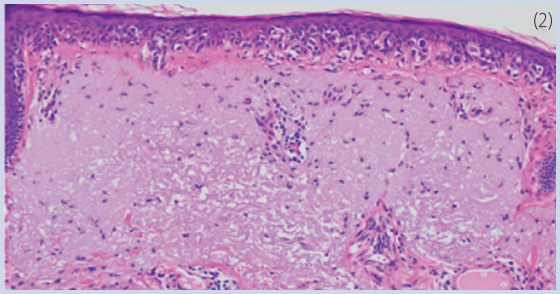
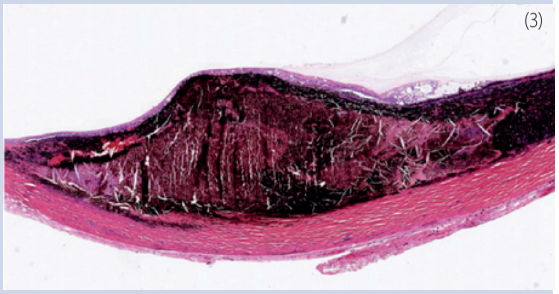
Another difficult group with respect to diagnostics comprises melanocytic lesions of the Spitz type, with their malignant form being Spitz melanoma/malignant Spitz tumour). A malignant form of melanocytic proliferations of the skin of the limbs is subungual melanomas of the limbs. Other types which have been distinguished are mucosal melanomas/genital, oral, sino-nasal melanomas), including mucosallentiginous melanomas and mucosalnodular melanomas. Melanomas

Table I. Division of the tumours arising from melanocytes according to the WHO classification from 2018

Melanocytic tumours in intermittently sun-exposed skin
low-CSD melanoma (superficial spreading melanoma)
simple lentigo and lentiginous melanocytic naevus
junctional naevus
compound naevus
dermal naevus
dysplastic naevus
naevus spilus
special-site naevi (of the breast, axilla, scalp and ear)
halo naevus
Meyerson naevus
recurrent naevus
deep penetrating naevus
pigmented epithelioid melanocytoma
combined naevus, including combined BAP1-inactivated naevus/ melanocytoma
Melanocytic tumours in chronically sun-exposed skin
lentigo maligna melanoma
desmoplastic melanoma
Spitz tumours
malignant Spitz tumour (Spitz melanoma)
Spitz naevus
pigmented spindle cell naevus (reed naevus)
Melanocytic tumours in acral skin
acral melanoma
acral naevus

Genital and mucosal melanocytic tumours
mucosal melanomas (genital, oral, sinonasal) mucosal lentiginous melanoma mucosal nodular melanoma
genital naevus
Melanocytic tumours arising in blue naevus
melanoma arising in blue naevus
blue naevus NOS
cellular blue naevus
mongolian spot
naevus of Ito
naevus of Ota
Melanocytic tumours arising in congenital naevi
melanoma arising in giant congenital naevus
congenital melanocytic naevus
proliferative nodules in congenital melanocytic naevus
Ocular melanocytic tumours
uveal melanoma epithelioid cell melanoma spindle cell melanoma, type A spindle cell melanoma, type B
conjunctival melanoma melanoma NOS
conjunctival primary acquired melanosis with atypia/melanoma in situ
conjunctival naevus
Nodular, naevoid and metastatic melanomas
nodular melanoma
naevoid melanoma
metastatic melanoma

Figure 1. Melanoma classification on the basis of the WHO recommendation from 2018 with reference to genetic changes

	Low UV exposure				High UV exposure				Low/ no/ varied UV exposure			
Type of malignant lesion	Low-CSD melanoma/superficial spreading melanoma				Melanomas chronically UV-exposed skin/ lentigo malignant melanomas	Desmoplastic melanoma	Malignant Spitz tumour (Spitz melanoma)	Subungual melanoma	Mucosal melanoma	Melanoma with congenital naevus	Melanoma with blue naevus	Uveal melanoma
	low-CSD melanoma/ superficial spreading melanoma – vertical growth phase [1]	combined BAP1-inactivated naevus/ melanocytoma	deep penetrating naevus	pigmented epithelioid melanocytoma								
Examples of histopathological images	 (1)				 (2)				 (3)			
Most frequent genetic changes												
BRAF p.V600e	+									+		
BRAF		+	+	+		+	+	+	+	+		
BRAF non-p.V600e					+							
NRAS	+	+	+		+	+		+	+			
HRAS							+	+				
KIT					+			+	+			
NF1					+	+		+	+			
CDKN2A	+				+		+	+	+			
TP53 and *PTEN*	+				+							
BAP1		+									+	+
TERT	+				+	+		+				
GNAQ, GNA11, CSLTR2											+	+

The most frequently occurring genetic changes are colour-coded: red – mutation of acquiring function, blue – mutation of the loss of function, purple – rearrangement, grey – promotor mutation, orange – amplification

can also be a malignant form of tumour arising in the blue naevus or rising in giant congenital naevus. A separate group is made by ocular melanocytic tumours, comprised of uveal melanomas and conjunctival melanomas. The last group is comprised of nodular melanomas, naevoid melanomas, and metastatic melanomas. The current classification of melanocytic proliferations is presented in table I.

The above classification specifies melanocytic proliferations in a traditional way, dividing them into benign and malignant lesions. Yet, as is the case with other tumours (for examples ovarian tumours or soft tissue carcinomas), the authors of the current classification "legalise" the terms which were previously used by dermatologists to describe the lesions with uncertain malignancy potential. This is the outcome of a belief that it is not always possible to definitely determine the potential of a lesion malignancy on the basis of morphologic features, immuno-profiling, and genetic changes.

The WHO classification from 2018 presents definitions and terms used for the description of melanocytic tumours of uncertain malignant potential (MELTUMP). Atypical melanocyte proliferation in the skin means that a lesion has the potential for vertical growth (tumorigenic), yet there are no definite criteria which would allow one to determine whether this lesion is benign or malignant. Also superficial atypical melanocytic proliferations of unknown significance *(*SAMPUS*)* were defined as atypical melanocytic proliferations localised in the epidermis and upper layer of the skin. Such a lesion cannot be definitely specified on the basis of a microscopic image, neither can the melanoma radial phase be excluded. In other words, SAMPUS is an atypical proliferation of pigment cells with the thickness of 0.8 mm, without ulceration in which deep maturation and symmetry are difficult to determine (which is understandable); also this proliferation lacks other typical morphological features typical for melanoma, such as mitotic activity. From a practical point of view, the therapeutic approach in both forms of melanocytic lesions is identical and consists of enlarging the surgical margin (the so-called wide resection of the scar). A differential diagnosis of SAMPUS is very difficult, especially when a skin specimen does not contain the entire lesion, is not optimally fixed or if there are some features of regression. It must be remembered that both "over-diagnosing" and "under-diagnosing" melanoma may lead to serious legal consequences for a pathomorphologist.

In the case of MELTUMP, there is always a chance that this is an atypical malignant proliferation of melanocytes which is potentially capable of producing metastases, and even life--threatening for a patient. To sum up, the term, "uncertain significance" in reference to the lesions of the SAMPUS or IAMPUS type (intraepidermal atypical melanocytic proliferation of uncertain significance) means only the possibility of a relapse or progression whilst the term "uncertain malignancy potential" in the case of MELTUMP means that a malignant course of the disease cannot be excluded. A differential diagnosis of MELTUMP always comprises a melanoma and histopathological assessment and should always contain a statement that, for example, this is "a lesion intermediate between a blue naevus and melanoma arising from a blue naevus".

The above diagnoses are descriptive and provisional, which means that one must always try to establish a precise and definite histopathological diagnosis. In a differential diagnosis, apart from a thorough microscopic assessment of the specimen routinely dyed with haematoxylin-eosin, the authors of the most recent classification recommend the use of immunohistochemical reactions, including HMB45, Ki-67 and p16. Immunohistochemical loss of the p16 protein usually signifies melanoma, yet in some cases, in which CDKN2A deletion does not occur within the melanoma ontogenetic pathway, a strongly preserved reaction with p16 is seen [7]. *BRAF* and *NRAS* gene mutations, frequently present in melanoma, are unfortunately also present in benign lesions. Therefore they do not have any diagnostic significance.

According to the 8th edition of the classification of pathological stages of melanoma (pTNM) worked out by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) from 2017, the assessment of a melanoma stage is based on two microscopic properties with the largest prognostic significance, i.e. the depth of infiltration and the presence of ulceration. The evaluation of an additional factor in pT1, i.e. mitotic activity in the vertical phase (present in the previous, 7th edition of the classification pTNM/AJCC/UICC) was abandoned. It must be emphasised that the correlation between mitotic activity and the frequency of metastases formation in lymph nodes was shown [6]. Yet, in comparison with the previous edition, the presence of the figures of cellular division in the vertical phase of thin melanomas does not mean the change of tumour stage from pT1a to pT1b. In spite of this, mitotic activity still remains a significant prognostic factor and should form a part of the histopathological diagnosis. Currently the "demarcation point" for thin melanomas is regarded to be a depth of 0.8 mm and with a lack of ulceration. From a clinical point of view, these lesions are treated as locally advanced and do not require the sentinel node procedure to be performed.

Table II. Primary melanoma staging with regards to T feature

pT	Lesion depth according to Breslow's classification
pT1a	Infiltration depth ≤0.8 mm, no ulceration
pT1b	Infiltration depth ≤0.8 mm, ulceration (+) or infiltration to the depth of 0.8–1 mm
pT2a	Infiltration depth >1–2 mm, ulceration (–)
pT2b	Infiltration depth >1–2 mm, ulceration (+)
pT3a	Infiltration depth >2–4 mm, ulceration (–)
pT3b	Infiltration depth >2–4 mm, ulceration (+)
pT4a	Infiltration depth >4 mm, ulceration (–)
pT4b	Infiltration depth >4 mm, ulceration (+)

Table II presents the stages of the primary melanoma according to the 8th edition of pTNM AJCC/UICC classification from 2017.

According to this classification, the pN stage specifies the melanoma metastases in lymph nodes (irrespective of their size and the number of tumour cells), microsatellite foci, satellite or in-transit metastases in lymph node(s) above 0 (pN > 0). In order to make a credible evaluation of lymph node status, at least six lymph nodes must be assessed. Not finding the melanoma metastasis in a lower number of the examined lymph nodes must also be classified as pN0 (like in the case of the evaluation of six or more lymph nodes). If no complete lymphadenectomy was performed, the histopathological report should contain a note that the classification is based only on the microscopic assessment of the sentinel node(s) – for example: pN0 (sn).

The current classification of the pN stage distinguishes the patients with clinically occult metastases. Such lesions, in a situation when no microsatellite or satellite foci or in transit metastases are found, are classified as N1a, N2a, N3a stage – depending on the number of the lymph nodes. When the above satellite foci or in transit metastases are present, yet without the metastases in the lymph nodes, the pN stage is qualified as N1c, N2c, N3c respectively – depending on the number of lymph nodes involved. But in the case of clinically evident metastases in the lymph nodes and without the presence of microsatellite or satellite foci or in transit metastases, the pN stage is evaluated to be pN1b, pN2b, pN3b – depending on the number of lymph nodes involved. In the 7th and 8th classification of TNM AJCC/UICC [8], the N stage is evaluated differently. However, the detection of a distant melanoma metastasis in a microscopic assessment is marked with the M1 symbol – as in the previous classifications.

The most recent WHO classification of skin cancers, similarly to the previous editions, emphasises the role of microscopic assessment. This classification presents detailed criteria, definitions, and terms used in the daily histopathological practice of assessing skin cancers, including melanoma. The pTNM AJCC/UICC classification, takes into consideration the role of the pathomorphological examination. This classification specifies the tumour stages based on significant prognostic factors. The update of the histopathological WHO classification and of the pTNM AJCC/UICC stages is the outcome of the developments in the studies of melanoma pathogenesis and epidemiological data.

All the microscopic parameters (apart from the histological type of melanoma) which have prognostic significance and which are useful for the selection of the treatment method, and which need to be obligatorily evaluated and stated in the histopathological report comprise: the depth of infiltration, the presence of ulceration and microsatellite or satellite foci or in-transit metastases. They determine the pTNM AJCC/UICC tumour stage.

Significant progress in access to new therapeutic methods of targeted therapies has been made in recent years; this has contributed to the increase in the importance of molecular tests – not only in the understanding of the process of oncogenesis, but also in the detection of predictive factors in personalised therapies. Therefore, a pathomorphological report should consider significant microscopic prognostic factors and predictive molecular markers.

Conflict of interests: none declared

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