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The Histopathological Diagnosis and Reporting of Melanoma: A New Look at an Old Challenge

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Abstract

The goal of a standardized and reproducible histopathological diagnosis and reporting of melanoma is far from being fully achieved. Clark's and McGovern's historical classification into lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma, and acral (and mucosal) lentiginous melanoma can be still kept as an acceptable startpoint. The WHO 2006 classification recognizes additional subtypes of melanoma but is still largely incomplete. The differential diagnosis of melanoma with benign melanocytic proliferations is one of the most difficult fields in Dermatopathology because it stems from the evaluation of a constellation of diagnostic criteria whose implementation, meaning, and relative weight considerably vary depending on the overall morphological context; thus the histopathological diagnosis of a melanocytic tumor is a mere *assessment of probability*, and is subject to considerable interobserver disagreement. Ancillary (Immunohistochemistry and molecular biology) techniques have been increasingly performed in order to assist the histopathological diagnosis; as a rule, however, no single information achieved with these techniques is expected to give clear-cut information for the differential diagnosis between nevus and melanoma. The histopathological reporting should include at least the following compulsory parameters: ulceration (absent vs present); mitotic rate (integer number/square millimeter); regression (if present); lymphovascular invasion (if present) perineurial invasion (if present); Breslow's thickness; microsatellitosis (if present); status of the surgical margins (with microscopically measured distances between tumor and lateral or deep margins). Even is molecular techniques are expected to completely change our landscape of histopathology of melanoma within the next few years; these 'classical' histopathological parameters are still the cornerstone for the management of melanoma patients.

Keywords: Melanoma; Histopathology; Differential diagnosis; Immunohistochemistry; Molecular biology; Histopathological reporting

Introduction

The histopathological diagnosis and classification of melanoma is probably the greatest conceptual and practical challenge in modern dermatopathology and is expected to rapidly evolve within the next few years [1]. For Clinicopathological purposes, it is still useful to refer to the time-honored classification proposed by Clark [2] in the United States and McGovern [3] in Australia, that is: lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma, and acral (and mucosal) lentiginous melanoma. However, we preliminarily warn that the clinicopathologic prognostic implications of such a classification are not so sharp as originally thought [4]. It must be also underlined that such 'classical' categories are identified by the microscopic features of the intraepidermal component of the neoplasm. When such an intraepidermal component is not associated with an invasive dermal component (melanoma cells breeching the basal membrane at the dermoepidermal junction), melanoma is defined as 'in situ' (confined within its anatomic compartment of origin). It should be noted that in the context of a seemingly in situ melanoma, invasive tumor is sometimes found after serial sectioning and immunohistochemical studies: however, standardized histologic protocols for the search of any invasive component in a putative melanoma in situ are still lacking.

Classical (Clark's And McGovern's) Subtypes of Melanoma

Lentigo maligna: This is the intraepidermal precursor/component of lentigo maligna melanoma. It typically occurs in chronically sun-exposed areas of elderly white patients and can be therefore considered as the melanocytic analog of actinic keratosis [4]. Microscopically, it s characterized by a lentiginous (that is: mainly a single cell) proliferation, mostly along the basal layer of the epidermis, with deep involvement of the adnexal structures; neoplastic melanocytes are mainly spindle and usually show an obvious nuclear pleomorphism. The proliferation of melanocytes in the depth of the adnexa may mimic invasion [5]. The dermis always shows severe solar elastosis (the histologic hallmark of severe and chronic sun damage); the epidermis is commonly atrophic. It has to be underlined that some exceptions to these rules do occur. It was emphasized that long-standing lesions of lentigo maligna may show a 'nested' architecture, [6] a nest being defined as an aggregate of at least three melanocytes. In our experience, the correlation between the age and the architecture of the neoplasm is not absolute; as a matter of fact, 43% of lentigo maligna cases have at least focal dysplastic nevus-like features, typified by nests arranged at the tips of elongated rete

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Table 1: Histological subtypes of melanoma according to the WHO 2006 Classification [17].

Diseases	Morphology Code
Superficial spreading melanoma	(8743/3)
Nodular melanoma	(8721/3)
Lentigo maligna	(8742/2)
Acral-lentiginous melanoma	(8744/3)
Desmoplastic and desmoplastic neurotropic melanoma	(8745/3)
Melanoma arising from blue nevus	(8780/3)
Melanoma arising in a giant congenital nevus	(8761/3)
Melanoma of childhood	
Nevoid melanoma	(8720/3)
Persistent melanoma	(8720/3)

Legend: In brackets is the morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (http://snomed.org).
Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for non-invasive tumours, and /1 for borderline or uncertain behaviour.

ridges [7]. Also based on Clinicopathological correlation, we have suggested that 'junctional atypical nevi' of the head-neck area in the elderly are indeed examples of 'nested lentigo maligna' and must be cautiously managed as such [8]. Once a dysplastic nevus has been excuded also on the basis of the Clinicopathological correlation, the main differential diagnosis of lentigo maligna is with subacute/chronic melanocytic photo activation, in which melanocytes are commonly epithelioid and monotonously atypical and show no nesting and no pigmentation (the latter being present in a cap-like fashion in the supranuclear region of the nearby keratinocytes) [9]. In recent years, also based on a careful Clinicopathological approach, a very slow-growing melanoma of the trunk, *lentiginous melanoma*, has been identified as the counterpart of lentigo maligna on non-chronically sun-damaged skin [10]. The neoplasm is usually very large; with a relatively regular ret form (dysplastic nevus-like) epidermal hyperplasia and a striking predominance of tightly packed single melanocytes at the junction [10].

Superficial spreading melanoma: is the most common subtype of melanoma and can occur anywhere in the body: [4] this means that the anatomic site of the neoplasm does not automatically identify the subtype. The equivalent term 'pagetoid melanoma'[3] elucidates the histopathologic hallmark of the intraepidermal component of the tumor, that is: the presence of melanocytes at all levels of the epidermis (pagetoid pattern); neoplastic cells are most often epithelioid (rather than spindle as in lentigo maligna and in acral lentiginous melanoma), and sometimes show a hypercromatic nucleus and an abundant pale cytoplasm with 'dusty' melanin (pagetoid cells): these features impart a 'shotgun appearance' to the epidermis. In some instances, however, the pagetoid configuration is made by relatively small cells and is at risk to being overlooked on histopathologic examination. It must be emphasized that pagetoid configuration is not invariably found in melanoma and is not pathognomonic of melanoma. A more or less prominent pagetoid scatter may be found in vulvar/genital nevi, acral nevi, recurrent/persistent nevi, Spitz/Reed nevi, in nevi of the childhood, and in several non-melanocytic tumors (Paget's disease, pagetoid Bowen's disease, tricholemmal carcinoma, epiderotropic T cell lymphoma, Merkel cell carcinoma, Langerhans cell histiocytosis). For a melanocytic tumor, in favor of a diagnosis of superficial spreading melanoma is the widespread pagetoid configuration, the pagetoid configuration at the edges of the tumor, and the cytologic atypia [11]. Epidermotropic metastasis of melanoma is also difficult to be differentiated from primary superficial spreading melanoma: [12] the anamnestic data and the Clinicopathological correlation are the mainstay for such a differential diagnosis.

Nodular melanoma: is defined by an intraepidermal neoplastic component which involves less than three rete ridges at the edges of a dermal tumor mass. Neoplastic melanocytes may be epithelioid or spindle; in addition, also nevoid melanoma and spitzoid melanoma (see below) should have, by definition, the typical architectural features of nodular melanoma. If identified according to strict Clinicopathological criteria, nodular melanoma is quite rare: [13] moreover, some cases fulfilling the criteria for nodular melanoma represent a *bona fide* advanced nodular phase of another subtype of melanoma; and some other cases labeled as nodular melanoma are possibly primary dermal melanomas [14]. The differential diagnosis between primary nodular melanoma and metastatic melanoma can be very difficult: in favour of primary nodular melanoma are the prominent involvement of the epidermis, the association with a nevus, and the presence of an epidermal 'collarette' at the edges of the neoplastic nodule.

Acral (and mucosal) lentiginous melanoma: It is characterized by an intraepidermal component of the lentiginous type with a striking predominance of spindle melanocytes with hypercromatic nuclei, mainly arranged in single units at the junction with variable (not always prominent) pagetoid spread [15]. The epithelium is typically hyperplastic, usually with thin and very elongated rete ridges; inflammation is often evident even in very early lesions as collections of lymphocytes at the tips of the rete ridges [16]. Tumors showing these features have been described in the volar skin, in the nail matrix, in the oral and nasal cavity, in the vulva, and in the anus [4]. Black and Orientals are most commonly affected by this subtype of melanoma in the skin.

Other Subtypes of Melanoma

The WHO 2006 classification of melanoma [17] (Table 1) encompasses, along with the 'classical' subtypes, the below specified entities.

Desmoplastic and desmoplastic neurotropic melanoma typically: (but not exclusively [18]) arises on chronically sun-damaged skin (head, neck, scalp) of the elderly. It is a spindle cell melanoma in which the malignant cells are separated by collagen fibers or fibrous stroma [17]. Lymphoid (lymphofollicular) nodules are a common key feature. When arising in chronically sun-damaged skin it often pushes solar elastosis into the deep dermis. Neurotropism (perineural or intraneural growth often exending far from the bulk of the tumor) is seen in at least 30% of cases [17].

The histopathological diagnosis can be very difficult because an atypical junctional component may be scanty or absent, cellularity may be low, and cytological atypia may be subtle. In addition, desmoplastic melanoma typically express only some immunohistochemical markers consistent with melanocytic lineage

(S100, p75/NGFr, SOX10) but is negative to the most commonly used panmelanocytic markers (MART1, HMB45, tyrosinase, MITF1) (see below) [19]. In order to define a melanoma as 'desmoplastic' the above-described immunomorphologic features must be present in >90% of the tumor mass; this is because desmoplastic features can be also detected as focal changes in other subtypes of melanoma ('combined' desmoplastic melanoma), as well as in recurrences and metastases from other types of melanoma [20].

Melanoma arising from blue nevus: is a primary dermal melanoma which arises in the context of a dermal dendritic cell proliferation (the so-called 'blue nevus family' [21]), most commonly a cellular blue nevus [22,23]. As expected, the most common anatomic locations of melanoma arising from blue nevus are the same as blue nevi (head/neck, trunk, buttock/sacrococcygeum) [22,23]. Histopathologically the neoplasm is typically biphasic with an abrupt transition from the benign to the overtly malignant counterpart. The commonly used synonyms 'malignant blue nevus' and 'blue nevus-like melanoma' have been source of confusion and should be probably restricted to dendritic cell malignancies devoid of any clear-cut benign component and characterized by non-traumatic ulceration, necrosis and/or mitotic rate >2/mmq [21].

Melanoma arising in a giant congenital nevus: should be intuitively defined as a melanoma arising either at the junction or within the dermis in the context of a giant (>20 cm in diameter [24]) congenital nevus [17]. In our experience, however, most if not all melanomas arising in giant or in large (11-20 cm in diameter [24]) are primary dermal malignancies which must be differentiated from the benign and atypical 'proliferative nodules' [25]. Different from proliferative nodules, dermal melanoma is most often larger than 5 mm and shows clear-cut features of malignancy (confluent pleomorphism, high mitotic rate, and necrosis): in addition, its margins are sharp and irregular with no evidence of 'merging' (the latter defined as a regular commistion between two different cell populations). Instead, melanomas arising within small (<1.5 cm [24]) or medium-sized (1.5-10 cm [24]) congenital nevi mostly arise at the dermoepidermal junction. Under the latter circumstance, the differential diagnosis from pagetoid scatter in 'atypical neonatal nevus' ('congenital nevus biopsied shortly after birth') [26] may prove virtually impossible on morphologic grounds alone: our personal suggestion is to consider as bona fide benign neoplasms all the atypical lentiginous or pagetoid proliferations detected in congenital nevi biopsied within the first year of life. The lifetime risk of melanoma in patients with non-giant congenital nevi has to be yet quantified with appropriate studies; in giant congenital nevi, the risk is approximately 2-5%, with most melanomas arising in the first decade of life [27,28].

Childhood melanoma: is an overtly malignant melanocytic tumor arising: i) in utero to the birth ('congenital melanoma'); ii) from the birth to one year of age ('neonatal melanoma'); iii) from one year of age to puberty ('childhood melanoma', *sensu strictiori*) [17]. It represents 0.4% of all melanomas, with very few well documented cases [29]. Childhood melanoma can be histopathologically sub classified into: i) conventional (adult-type); ii) small cell (resembling a lymphoma or another small round blue cell malignancy); iii) resembling Spitz nevus [17]. The most controversial category is the last one. There is no doubt that a small percentage of the so called 'atypical Spitz tumors' of the childhood do metastasize and, *ex post*, can be labeled 'Spitzoid melanoma'; it is also true, however, that a clear-cut histopathological differentiation between metastasizing and non-metastasizing cases has been proven to be virtually impossible [30]. We personally restrict the term 'Spitzoid melanoma of the childhood' to cases characterized by an overtly malignant, non-Spitzoid melanocytic clone developing in the background of a Spitzoid neoplasm [31,32].

Nevoid melanoma: is a subtype of nodular melanoma mimicking the architectural features of a common compound or intradermal nevus. It was originally described by Schmoeckel et al in 1985 in a series of 33 patients, 15 of which developed metastatic disease and 8 of which ultimately died of disease [31]. Nevoid melanoma is the 'triggered trap' in Dermatopathology: [33] because of its striking resemblance to a banal nevus at the scanning magnification, the correct diagnosis is based on a high index of suspicion, as well as on a careful evaluation of the cytomorphologic details. Two histopathological variants can be recognized, namely: the verrucous (papillated) and the nodular/plaque-like (non-papillated). In the elderly, the verrucous silhouette is suspicious *per se*. histopathologically; there is a confluent growth of melanocytes, often in vertically-oriented sheets. The junctional component can be minimal or even absent, especially in the nodular variant; on the contrary, however, there can be effacement of the epidermis and loss of the sub epidermal 'grenz zone'. Cytomorphologically, even if there is 'pseudomaturation' (progressive reduction of the size of the nests and of the cells from the surface to the depth), pleomorphism and mitotic figures, even in the deep portion of the tumor, are almost invariably seen [34]. Ancillary techniques, mainly the immunostain for the cell cycle associated protein Ki67 (evidence of irregularly distributed positive cells in clusters and/or within the deep portion of the tumor) can assist the diagnosis [35].

The WHO 2006 classification considers also Spitzoid melanoma (of the adulthood) as a variant of nevoid melanoma composed of medium-sized to large Spitzoid melanoma cells; [17] of course, the boundary between an atypical Spitz tumor and a Spitzoid melanoma is at least burred, if not highy subjective.

Persistent melanoma: is defined by the persistent growth of an incompletely excised primary melanoma. It usually presents as a tumor extending beyond the surgical scar in the same growth pattern as the tumor left on the surgical margin(s) of the previous (excision) specimen. The host response, in terms of both inflammation and fibrosis is often prominent. Persistent melanoma must be distinguished from recurrent nevus [36] and from local (in-transit) metastasis of completely excised melanoma [37]. As a rule, a nevus recurs within a few months after its incomplete excision; both clinically and histopathologically it is centered on the scar; a typical trizonal pattern is histopathologically identifiable, namely: an atypical, usually heavily pigmented junctional component, a wide area of dermal fibrosis, and a bland-appearing deep dermal melanocytic component [36]. On the contrary, local metastasis of melanoma usually presents several years after excision of the primary as multiple nodules also at distance from the scar. Also histopathologically, the growth pattern is frequently multinodular; vascular invasion is frequent; the host response is commonly absent. These features are not observed in persistent melanoma [17].

Table 2: Other histological variants of melanoma.

'Invisible' (achromic) melanoma	Epitheliomorphic neoplastic cells with no melanin deposition; not uncommon as an in situ neoplasm on chronically sun-damaged skin
Small-diameter melanoma	A melanoma whose breadth is <6 mm (<4.7 mm after formalin fixation)
Nested melanoma (of the elderly)	Junctional proliferation almost exclusively composed by large and irregular nests
Primary dermal melanoma	Melanocytic tumor in dermis or sub cutis with no in situ component (regression of the intraepidermal component or derivation from non-epidermal melanocytes)
Polypoid/exophytic melanoma	Cauliflower-like pattern; cytologic atypia usually striking
Verrucous melanoma	Melanoma with a prominent papillated epidermal hyperplasia
Follicular melanoma	Neoplastic growth centered on 1-3 hair follicles; length of the epidermal involvement to each side of the affected hair follicle(s) not exceding the depth of the follicular structure
Minimal deviation melanoma	Possibly a variant of nevoid melanoma, with a minimal histological deviation from a'common' or a 'dysplastic' nevus
Halo nevus-like melanoma	A melanoma with a prominent lichenoid lymphocytic infiltrate and with a silhouette resembling a 'halo nevus'
Small cell melanoma	Small tumor cells, with minimal cytoplasm, round hyperchromatic nuclei and prominent nucleoli.
Signet ring melanoma	Tumor cells with pale cytoplasmic globular inclusions pushing the nucleus at the periphery.
Rhabdoid melanoma	Large epithelioid tumor cells howing an abundant inclusion-like eosinophilic cytoplasm.
Balloon and clear cell melanoma	Tumor cells with an abundant clear cytoplasm with fine granular or vacuolar changes.
Myxoid melanoma	Tumour cells interspersed within an intercellular matrix made by a basophilic, PAS negative and Alcian blue positive mucinous material.
Melanoma with neuroendocrine features	Carcinoid-like pattern; paraganglioma-like pattern; neuroblastoma-like pattern. Possible immunohistochemical expression of chromogranin and synaptophysin, with or without the above-detailed morphologic features
Pseudovascular melanoma	Angiotropic melanoma cells around and infiltrating vessel walls, or: angiomatoid changes with blood-filled spaces reminiscent of angiosarcoma.
Sarcomatous (spindle cell) melanoma	A spindle cell malignant tumor; often showing loss of some panmelanocytic markers
Pseudolymhomatous melanoma	Melanoma with prominent lymphoid cell infiltrate; melanoma cells with some degree of cohesiveness (lymphoepithelioma-like pattern)
Bullous/Acantholytic melanoma	Junctional confluence of dyscohesve melanocytes creating a bullous cleft
Melanoma with multinucleated giant cells	Touton-like, osteoclast-like, or pleomorhic giant cells interpersed within the tumor mass
Melanoma with monster cells	Tumor cells of gigantic size
Metaplastic melanoma	Melanoma with metaplastic elements such as bone, cartilage and smooth muscle.
Atypical fibroxanthoma-like melanoma (melanoma with a 'null' immunophenotype)	Melanoma with complete loss of pan-melanocytic immunohistochemica markers
BAP-1 mutation associated melanoma	Melanoma cells with somewhat Spitzoid cytmorphologic features resulting from biallelic inactivating mutation of the BAP-1 gene on 3p21.1; diagnosis confirmed by a negative nuclear immunostain for the BAP-1 protein in neoplastic cells

Other subtypes of melanoma: are not listed in the WHO 2006 classification and are given in (Table 2). The identification of some of these subtypes might be prognostically relevant: for example, BAP-1 mutation-associated melanoma could behave in an indolent fashion (Dr. Thomas Wiesner, personal communication)

Histopathological Diagnosis

Optimal evaluation of any melanocytic lesion requires complete excision that incorporates the full thickness of the involved lesion removed intact. "Shave" procedures that do not include the intact base of the lesion should be avoided. Similarly, "punch" procedures suffer from limitations due to the 'sampling' of the lesions and must be therefore restricted to the preoperative differential diagnosis between melanocytic and non-melanocytic lesions whose *in toto* excision would lead to cosmetic and/or functional impairment.

The recognition of a melanocytic tumor as it is not based upon the search of a single (or a few), objective and easily reproducible morphological diagnostic feature(s) but, instead, it is born by a constellation of diagnostic criteria whose implementation, meaning and relative weight considerably vary case by case. For example, it has been thoughtfully speculated that using for Spitzoid melanocytic tumors the same diagnostic criteria as for 'conventional' (non-Spitzoid) melanocytic tumors is a conceptual and practical mistake [38]. For these reasons, the histopathological diagnosis, being based upon the simultaneous evaluation of several criteria, is no more than an *assessment of probability* and, as such, is often matter of a sizable disagreement and inter-observer variability [39]. (Table 3) summarizes the main differential criteria between nevus and melanoma.

Because of the lack of objective and reproducible diagnostic criteria, ancillary techniques have been increasingly implemented in routine practice. Among these, Immunohistochemistry is the most widely used (Table 4). It is aimed at:

1. The demonstration of a melanocytic histogenesis for undifferentiated (anaplastic) malignancies in their either primary cutaneous or metastatic site.

2. The recognition of nodal melanocytic deposits in sentinel node biopsy.

3. The identification of prognostic factors (comprising Breslow's thickness) in melanoma.

4. The differential diagnosis among benign and malignant melanocytic tumors in the skin.

Table 3: Histopathological criteria for the differential diagnosis between nevus and melanoma.

NEVUS	MELANOMA
ARCHITECTURAL CRITERIA	
SIZE	
With the exception of congenital nevi, a nevus is seldom larger than 8 mm	A diameter >8 mm is the rule
SYMMETRY	
Nevi are symmetric: an ideal perpendicular line passing through the centre of the lesion divides the tumor into two secularly similar halves	Melanomas are asymmetric
PIGMENT DISTRUBUTION	
Melanin is uniformly distributed and, with the exception of dermal dendritic melanocytic tumours, mainly confined within the superficial part of benign lesions	Melanin is irregularly distributed; largely amelanotc tumours can show pigment synthesis in the depth
NESTS	
Uniformly sized, shaped, and spaced junction nests prevail over single cells. In Spitz nevus and in 'dysplastic' nevus there can be focal junctional fusion ('bridging') of nests.	Single cells prevail over nests; the latter are irregularly sized, shaped, and spaced; junctional fusion of nests is irregular
CYTOLOGICAL CRITERIA	
CELL DISTRIBUTION	
Monotonous cell population; regular spacing of the nuclei; same cell population at the same level of both the epidermis and the dermis	Hypercellularity, crowding/overlapping of nuclei; different cell populations at the same levels of the epidermis and/or of the dermis
MITOSES	
Few and confined within the superficial part of the lesions	Common; superficial and deep; often within the 'proliferation belt' (within 0.25 mm from the growing edge of the tumor in the dermis)
ATYPIA	
Absent; 'random' (non-confluent) in Spitz nevus	Present, confluent
NECROSIS	
Absent	Present.
MATURATION	
Progressive reduction of the cell size with the descent into the dermis: epithelioid (type A) melanocytes at the junction; lymphocyte-like (type B) melanocytes within the superficial dermis; neuroid (type C) melanocytes within the deep dermis	The cell size does not significantly change from the surface to the depth; different cell clones at the same levels; no neuroid melanocytes in the depth
PAGETOID CONFIGURATION	
Absent or confined within the central portion of the lesion	Present, irregularly distributed, also close to the lateral edges of the tumor
DERMOEPIDERMAL CHANGES	
EPIDERMIS	
Regular hyperplasia: thin and elongated rete ridges in 'dysplastic' nevus; broad rete ridges with overlying hyperkeratosis/hypergranulosis in Spitz nevus	Flattening of the dermoepidermal junction; atrophy; consumption; ulceration. Possible irregular hyperplasia
CLEFTS	
In Spitz nevus, half-moon shaped, with sharp separation of the junctional nests from the nearby keratinocytes	Irregular clefts; horizontal clefts
KAMINO BODIES	
In Spitz nevus: large, dull-pink, numerous, sometimes pigmented	If present, few in number and small in size
ADNEXA	
Terminal hair with 'hamartomatous' features; hyperplastic sebaceous glands; folliculocentric growth	Terminal hair absent; adnexotropic growth
ELASTIC FIBERS	
Hyperplastic; slight or no sun damage	Elastic fibres destroyed and compressed at the base of the proliferation; marked sun damage
INFLAMMATION	
Patchy, perivascular. In nevus of Sutton, a broad and symmetric band of lymphocytes involving the entire length of the lesion	Lichenoid, asymmetric. Associated with regression (fibrosis, melanosis, newly formed vessels). 'Skip' areas (areas of seemingly normal skin within the neoplasm)

The first three goals can be achieved with the use of 'panmelanocytic markers': the best approach is to use S100, which is the most sensitive and less expensive marker, plus one more specific lineage-specific marker (MelanA/MART1, tyrosinase, MITF1, p75/NGFr, or SOX10) In our opinion, the most efficient and less expensive couple of reagents are S100 and MelanA/MART1, but with two main caveats: i) desmoplastic melanoma is negative to MART1, tyrosinase, and MITF1 and can be identified solely with the anti p73/nerve growth factor receptor antibody, or with the anti SOX10 antibody; [19] ii) on sun-damaged skin, a nuclear marker (MITF1 or SOX10) should replace MelanA/MART1, which can give a melanoma-like staining pattern by labeling either hyperplastic dendrites or 'pseudomelanocytic nests'

Table 4: Immunohistochemical markers of melanoma (adapted from de Vries, et al [17]).

Functional category	Markers
Differentiation	Tyrosinase, TRP-1, AIM-1 Mitf, gp100 (HMB45), TRP-2, S-100, HMW-MAA, Melan-A/MART-1, MC1R
Proliferation	Cyclin A ↑ Cdk2 ↑ p21 ↑ PCNA ↑ Cyclin B1 ↑ p15 ↓p16 ↓p27 ↓ mdm-2 ↑Cyclin D1/D3 ↑ Ki67 ↑ Telomerase ↑Cyclin E ↑pRB ↓
Apoptosis	Survivin ↑p53 ↑bcl2 ↑BAX ↑
Signalling	c-Kit ↓ N-ras ↑ EGFR ↑ PTEN ↓c-Myc ↑ α-catenin ↓ Transferrin receptor ↑
Transcription	ATF-1 ↑ AP-2 ↓
Adhesion	E-Cadherin ↓ ICAM-1 ↑ ALCAM ↑ α4ß1 ↑N-Cadherin ↑ MCAM ↑ αvß3 ↑ CD44 v6 ↑VCAM-1 ↓Galectin 3 ↓
Proteases	MMP-1 ↑ MMP-13 ↑ TIMP-3 ↑ PA-system ↑MMP-2 ↑ MT1-MMP ↑ EMMPRIN ↑ Cathepsin B, D, H, L ↑MMP-9 ↑ TIMP-1 ↑
Other	ME491/CD63 ↓ HLA class I ↓ HLA Class II ↑ CTAs ↑Osteonectin ↑ Fas/Fas ligand ↑COX2 ↑WT1↑

Legend: ↑ Up regulation with tumor progression; ↓ down regulation with tumor progression.

Table 5: Molecular investigations for melanoma diagnosis.

Technique	Expected results in melanoma
(Array) Comparative Genomic Hybridization	Gains at 1q, 6p, 7p, 7q, 8q, 17q, 20q, 4q, 8q, and 11q. Losses at 6q, 9p, 10p, 10q, 11q, and 21q
Fluorescence in situ hybridization	RREB1 gain>29%; RREB1 gain relative to Cep6>55%; CCND1 gain >38%; MYB loss relative to CEP6>31%; MYC gain >29%; CDKN2A biallelic loss relative to Cep9 >29%
Gene expression profiling	Compared with nevi, different expression of a set of genes including PRAME, S100A7, S100A8, S100A9, S100A12, PI3, CCL5. CD38, CXCL9. CXCL10, IRF1, LCP2, PTPRC, SELL
DNA sequencing	In familial melanoma: mutations of CDKN2A (40%), MITF (20%), CDK4, BAP1, TERT, POT1 In sporadic melanoma: mutations of BRAF (53-66%), NRAS (9-29%), KIT (36% of acral melanomas; 88% of oral melanomas), GNAQ (50% of uveal melanomas)
DNA methylation profiling	Methylation of promoters of CDKN2A, PTEN, RASSF-1A, RASSF10, RAR-beta2
Micro-ribonucleic acid (MiRNA) profiling	Up regulation of miRNA192; down regulation of miRNA132
Mass spectrometry	Actin, vimentin, and three unknown peptides differently expressed in Spitz nevi and Spitzoid melanoma

of keratinocytes involved in a lichenoid tissue reaction [40].

Lineage-specific markers can be also used to refine the measurement of Breslow's thickness (see below) of melanoma. Cases of melanoma with halo-reaction and/or regression can show 'blurred' deep margins: therefore, Immunohistochemistry can highlight deeply entrapped melanocytes thereby avoiding under-micro staging [41]. Mitotic rate is a strong prognostic indicator in melanoma; in addition, the 2010 American Joint Committee on Cancer (AJCC) 7 staging system has replaced Clark's level IV (see below) with mitotic rate ≥1/mmq to define pT1b melanoma and to select patients for sentinel node biopsy [42]. Immunodetection of phosphohistone H3 protein has been shown to facilitate the identification of mitotic figures and to refine micro staging of thin (≤1 mm) melanoma [43].

The differential diagnosis between benign and malignant melanocytic tumors is the most ambitious task for Immunohistochemistry. Data on this topic have been continuously updating [35]. After a review of the pertinent literature (unpublished observation), we have realized that an acceptable compromise between cost, increase in technical routine workload, and diagnostic impact is the adoption of an antibody panel composed as follows:

a. the anti cell cycle-related protein Ki67. Its staining can be evaluated either with a systematic count of neoplastic cells (<5% of neoplastic cells labeled in common nevi; 5-13% of neoplastic cells labeled in 'dysplastic' nevi and Spitz nevi; >13% of neoplastic cells labeled in melanoma) or with an 'eyeballed' evaluation of the staining pattern (tidy in nevi; untidy with clusters of proliferating cells in melanoma) [35,44].

b. the anti human melanoma black (HMB)45. Its expression recalls the 'maturation' of nevi (progressive loss of reactivity from the surface to the depth) and the architectural disorder of melanoma ('patchy' reactivity, with isolated or clustered cells being labeled throughout the dermis) [35,45].

c. the anti p16 protein. This antibody stains nevi in an either strong and diffuse or a tidy ('checkerboard') pattern; instead, melanomas typically show confluent foci of complete loss of reactivity; [45,46]. In our experience, desmoplastic melanocytic proliferations are the main morphologic setting in which the p16 immunostain can assist the diagnosis.

Unfortunately, the above illustrated rules have relevant exceptions and limitations. For example, the HMB45 immnoreactivity is lost in melanoma progression, as well as in the presence of a heavy lymphocytic infiltrate; [47] on the other hand, benign dermal dendritic melanocytic proliferations are strongly and diffusely HMB45 positive and a focal loss of reactivity can be a clue to malignancy [35]. It must be therefore emphasized that Immunohistochemistry must be always evaluated within the morphological context; and that not any single immunostain is able to give clear-cut information for the differential diagnosis between nevus and melanoma.

Molecular techniques are being increasingly proposed with the aim of looking for specific pathways toward melanoma genesis. (Table 5) lists the main techniques under investigation along with the main (expected) findings. We underline that:

a. when matched with morphologically obvious melanocytic tumors, all these techniques shows a greater specificity than sensitivity, thereby 'ruling in' and not 'ruling out' melanoma;

b. most if not all of the molecular pathways investigated

Table 6: Problems in the measurement of Breslow's thickness.

Melanoma subtype	Suggested strategy
Nevus-associated melanoma	Perform Immunohistochemistry (antiKi67, anti HMB45, anti p16); if still in doubt, report the greatest value of thickness with a statement about a possible overestimation due to the (possible) association with a nevus
Halo nevus-like melanoma; melanoma with regression	Perform Immunohistochemistry (at least two panmelanocytic markers: see text) for the detection of neoplastic cells entrapped in the depth by the host response to the tumor
Verrucous melanoma	Pick a point halfway between the base and apex of a papillation and measure from there to the deepest melanoma cells
Follicular melanoma	Draw an ideal vertical line passing through the centre of the hair follicle and measure the thickest half of the tumor perpendicular to this line
Bullous/acantholytic melanoma	Detract the thickness of the bullous detachment from the total thickness

thus far are shared by morphologically benign, morphologically ambiguous, and morphologically malignant neoplasms, and this hampers the diagnostic importance of the molecular findings.

Histopathological Reporting of Melanoma

The histopathological report must include all the pertinent clinical information and a thorough macroscopic description comprising the sampling protocol adopted. A microscopic description of the tumor, as well as the implementation and the results of the ancillary techniques are optional if the final diagnosis is clear-cut.

Compulsory histopathologic parameters include the following:

A. Ulceration (present vs absent). It is defined as a full-thickness epidermal defect above dermal melanoma growth, with reactive tissue changes (fibrin, neutrophils) and atrophy or hypertrophy of the surrounding epidermis, with no history of trauma or surgery [48].

B. Mitotic rate. The suggested method of evaluation is the so-called 'hot spot': after finding the areas of the dermis containing most mitotic figures, the count is extended to adjacent fields up to covering an area corresponding to 1 mmq (4 microscopic fields at a 400x magnification); in the absence of an identifiable hot spot, a representative mitosis is sought and the count is extended to the adjacent fields up to a 1 mmq area [42]. The mitotic rate should be given as an integer number; if no mitotic figure is found in the invasive component of the tumor, the mitotic rate must be given as 0/mmq.

C. Regression (if present). It is defined as a replacement of a portion of dermal tumor tissue by fibrosis with newly formed vessels and a variable amount of lymphocytes and melanophages. It can be focal (involving a portion of invasive tumor), partial (involving the entire invasive tumor), or complete (involving the entire tumor) Since complete regression and regression involving more than 75% of the lesion has been reported to carry adverse prognostic importance in invasive melanoma, [49] it is recommended to assess regression, if present, as: i) involving up to 75% of the tumor mass; ii) involving more than 75% of the tumor mass; iii) involving the entire tumor (complete).

D. Lymphovascular invasion (if present). The immunostain for an endothelial marker (CD31, podoplanin) can help the assessment [50].

E. Perineurial invasion (if present). Since melanoma is typically S100-positive as are also nerves, an immunostain for the perineural sheath with the anti-Epithelial Membrane Antigen (EMA) or, else, with the anti-Glut1 can be used to individuate the nerve fibers.

F. Breslow's thickness. Maximum tumor thickness is measured with a calibrated ocular micrometer at a right angle to the adjacent normal skin. The upper point of reference is the granular layer of the epidermis of the overlying skin or, if the lesion is ulcerated, the base of the ulcer. The lower reference point is the deepest point of tumor invasion (i.e., the leading edge of a single mass or an isolated group of cells deep to the main mass). If the tumor is transected by the deep margin of the specimen, the depth may be indicated as "at least _ mm" with a comment explaining the limitation of thickness assessment. Special problems in the measurement of Breslow's thickness are illustrated in (Table 6).

G. Microsatellitosis (if present). It is defined as the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow's measurement was taken [51]. It is also recommended to include microsatellites into Breslow's thickness itself.

H. Status of the surgical margins. Microscopically measured distances between tumor and labeled lateral or deep margins are appropriately recorded for melanoma excision specimens because these neoplasms may demonstrate clinical "satellitosis." Nevertheless, a "safe minimum" margin has not been established in the literature. If a lateral margin is involved by tumor, it should be stated whether the tumor is in situ or invasive.

Optional parameters of the histopathological report are the following:

a. Histological subtype. This can be considered as an optional parameter because the current classification of melanoma evaluates a sum of criteria which are neither purely histopathologic nor exclusively tumor-related; therefore, features of different subtypes can be present in a given tumor, and, conversely, different subtypes of tumor can have similar histopathologic features. Even more important, the prognostic and therapeutic value of the current classification is probably minimal [4].

b. Clark's level. This is defined as follows:

I - Intraepidermal tumor only

II - Tumor present in but does not fill and expand papillary dermis

III - Tumor fills and expands papillary dermis

IV - Tumor invades into reticular dermis

V - Tumor invades sub cutis

Anatomic level has been replaced by mitotic rate in the AJCC 7th edition tables for sub classifying pT1 lesions as T1a or T1b, but in the text and in a table comment of the AJCC chapter, [42] Clark level IV or V is referred to as a tertiary criterion for T1b in cases with no ulceration and "if mitotic rate cannot be determined". Clark level should therefore be reported whenever it would form the basis for upstaging T1 lesions.

c. Tumor growth phase, radial (horizontal) vs vertical. In radial (horizontal) growth phase, the tumor demonstrates a uniform cytological appearance and is generally wider than it is deep; a commonly applied criterion is presence of melanoma in situ three or more rete ridges beyond the invasive component. Vertical growth pattern in superficial spreading melanoma is defined as the presence of one or more dermal clusters larger than the largest epidermal cluster and/or the presence of any mitotic activity in the dermis [52]. Nodular melanomas are by definition vertical growth phase tumors.

d. Tumor-infiltrating lymphocytes. A paucity of tumor-infiltrating lymphocytes (TILs) has been reported as an adverse prognostic factor for cutaneous melanoma [49]. To qualify as TILs, lymphocytes need to surround and disrupt tumor cells of the vertical growth phase. Thus, the criterion does not apply to melanoma in radial (horizontal) growth phase. TILs are scored as: i) not identified: lymphocytes not present in the examined tissue sections, or: lymphocytes present but not infiltrating the tumor; ii) nonbrisk: lymphocytes infiltrating melanoma only focally or not along >90% of the base of the vertical growth phase. iii) Brisk: lymphocytes diffusely infiltrating >90% of the base of the vertical growth phase.

Conclusion

The proper diagnosis and classification of melanoma is still a great challenge in modern Dermatopathology. Even is molecular techniques are expected to completely change our landscape of histopathology of melanoma within the next few years, conventional morphology remains the undisputable mainstay for the diagnosis?

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