Uncommon Histopathological Variants of Malignant Melanoma: Part 1

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Abstract: Despite new horizons opened by recent advances in molecular pathology, histological evaluation still remains the diagnostic gold standard regarding cutaneous melanocytic neoplasms. Several histological variants of melanoma have been described, and their knowledge is crucial for accurate diagnosis and classification of cases with unusual clinicopathological features. Uncommon histological variants of melanoma have been described based on a broad constellation of features, including architectural pattern, stromal alterations, cytological attributes, and other morphological properties. This review is aimed at providing an extensive discussion of unusual but distinctive histopathological variants of melanoma.

Key Words: melanoma, pigmented epithelioid melanocytoma, animal-type melanoma, plexiform melanoma, spitzoid melanoma, balloon cell melanoma

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LEARNING OBJECTIVES

After participating in this activity, the physician should be better able to:

1. Analyze different types of melanocytic tumors regarding architectural, cytomorphological, and immunohistochemical features.
2. Assess the histopathological pattern of different types of melanoma with particular regard to specific variants characterized either by the presence of peculiar cell types (eg, balloon cells, multinucleated cells, signet-ring cells, etc.), by unconventional morphology (eg, follicular melanoma, bullous melanoma, small melanoma, etc.), or by stromal changes (eg, desmoplasia).
3. Distinguish between several melanoma variants with peculiar structural features and recognize challenges related to measurement of tumor thickness.

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Despite new horizons opened by recent advances in molecular pathology, histological evaluation still remains the diagnostic gold standard regarding cutaneous melanocytic neoplasms.[1–3] In addition to main melanoma categories listed in the WHO classification of tumors (Table 1),[4] several other histological variants have been described, and their knowledge is crucial for accurate diagnosis and classification of cases with unusual clinicopathological features.[5,6] Uncommon histological variants of melanoma have been described based on a broad constellation of features, including architectural pattern, stromal alterations, cytological attributes, and other morphological properties.[7,8]

This is the first part of a review aimed at providing an extensive discussion of unusual but distinctive histopathological variants of melanoma, as described in the available literature. For practical purposes, histological entities are listed according to alphabetical order.

ANGIOMATOID MELANOMA

The term "angiomatoid melanoma" has been coined for tumors of malignant melanocytes characterized by a low-power silhouette distorted by the presence of variably large spaces filled with erythrocytes (Fig. 1).[8,9] First reported in metastatic lesions of melanoma,[9] the angiomatoid pattern may also be found in primary tumors.[10,11] Histopathologic evidence of hemorrhagic spaces in angiomatoid melanomas may be associated with clinical features suggestive of a vascular neoplasm/malformation.[8] Of note, most primary angiomatoid tumors reported in the literature to date have been thick melanomas with dismal prognosis.[10]

Histopathologically, irregular hemorrhagic, pseudovascular, cavernous-like spaces seem to separate melanocytic complexes, with single cells and/or small cellular aggregates apparently floating within hemorrhagic areas.[8,10] These spaces are not true vessels, being rather lined by neoplastic melanocytes, as proved by immunohistochemical staining for melanocytic and endothelial markers[8]; indeed, the term "pseudovascular" has also been used to describe cases with an analogous histologic picture.[8,10] In this context, it should be reminded that focal positivity for podoplanin in neoplastic melanocytes may be observed in otherwise conventional melanoma.[10] Expression of additional vascular antigens (such as CD31, ERG, and FLI-1) should be investigated in dubious cases to avoid potential pitfalls. Although the pseudovascular

TABLE 1. Malignant Melanocytic Tumors According to the New WHO Classification[4]

Pathway I	Low UV melanoma/superficial spreading melanoma
Pathway II	High UV melanoma/lentigo maligna melanoma
Pathway III	Desmoplastic melanoma
Pathway IV	Malignant Spitz tumor
Pathway V	Acral melanoma
Pathway VI	Mucosal melanoma
Pathway VII	Melanoma in congenital nevus
Pathway VIII	Melanoma in blue nevus
Pathway IX	Uveal melanoma
Variable pathways	Nodular melanoma

UV, ultraviolet radiation–associated skin changes.

spaces are not true vessels, transcriptional reprogramming with activation of angiogenetic networks is a well-known occurrence in advanced, usually metastatic melanoma[12,13]; such phenomenon, aimed at increasing perfusion of tumor cells, may lead to a hybrid phenotype with coexpression of melanocytic and vascular markers.[12,13]

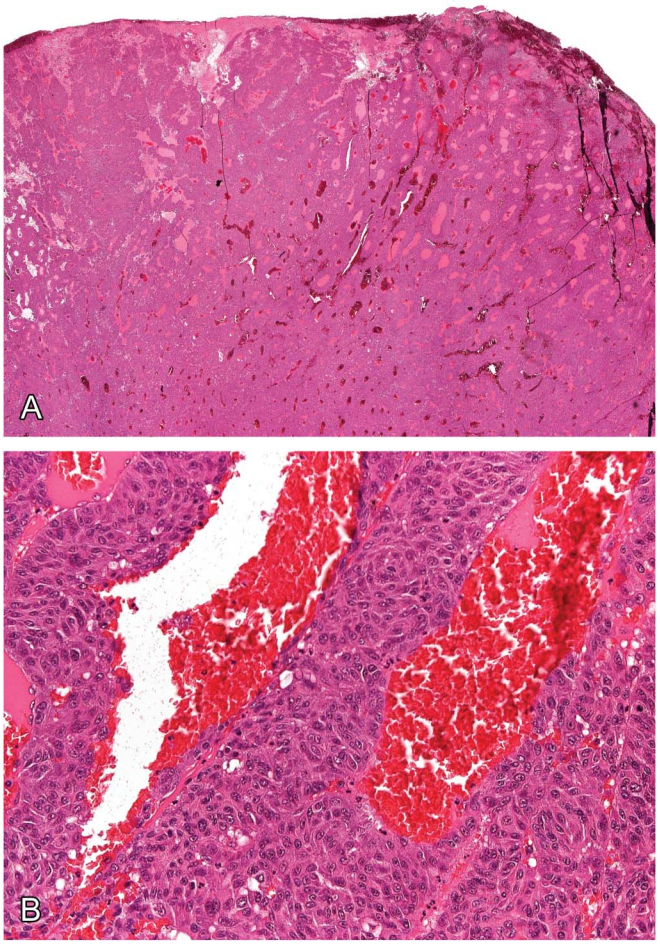

FIGURE 1. Angiomatoid melanoma. A, Large, thick melanoma with numerous pseudovascular spaces filled with erythrocytes. B, Detail of the pseudovascular spaces surrounded and lined by neoplastic cells of the melanoma.

"ANIMAL-TYPE" MELANOMA (PIGMENT-SYNTHESIZING MELANOMA)

Animal-type melanoma belongs to the broad, heterogeneous group of "pigment-synthesizing" melanomas.[14–16] Striking clinical features reminiscent of a peculiar, heavily pigmented melanocytic tumor typical of gray Lipizzaner horses had initially prompted the use of this term,[17] although it has been later recognized that such equine neoplasm has different biological properties than this peculiar variant of melanoma observed in humans[18]; hence, animal-type melanoma is a misnomer.[18] Several other terms have been variably used referring to this entity, including "melanoma with prominent pigment production" and "equine-type melanoma," among others.[14–16] The combination of striking melanin deposition and relatively indolent behavior has led several authors to abandon the denomination animal-type melanoma in favor of the umbrella term "pigmented epithelioid melanocytoma," under which several heavily pigmented melanocytic tumors have been variably lumped (see later).[16,19,20] With the proviso that a certain degree of confusion persists in this regard, the following discussion will be limited to lesions referred to in the past as animal-type melanoma, with the caveat that significant biological overlap with other neoplasms currently classified as pigmented epithelioid melanocytoma may exist.

Clinically, animal-type melanoma usually occurs in the adult population, presenting as a dark plaque/nodule larger than 1 cm in diameter.[14,18,21] The limbs are the most common site of occurrence, followed by the head and neck area and the trunk.[15,22] Histopathologically, animal-type melanoma is characterized by nodular aggregates of heavily pigmented melanocytes intimately intermingled with large numbers of melanophages, with the latter often representing the predominant cell population (Fig. 2).[14,16,18] Cytologically, epithelioid, spindle, and dendritic melanocytes were variably present, frequently exhibiting mild to moderate atypia.[15,18] According to Zembowicz et al,[19] epithelioid cells tend to occupy the central portion of the neoplasm, with spindled melanocytes being more numerous at the periphery and showing an infiltrative arrangement. Ulceration and intraepidermal pagetoid spread of melanocytes are rarely, if ever, observed; neither perineural growth nor lymphovascular are described in reported cases.[16,18,19] Of note, it should be reminded that focal nodules of heavily pigmented melanocytes may be found in conventional types of melanoma[16]; care should be taken not to classify such cases as animal-type melanoma or pigmented epithelioid melanocytoma (Fig. 3).

Based on limited retrospective data available in the literature, animal-type melanoma may be regarded as a low-grade variant of melanoma, characterized by frequent locoregional nodal involvement but only limited metastatic potential.[14,15,22] Furthermore, age seems to play a prognostic role in animal-type melanoma, with detection of a positive sentinel node being significantly associated with older age.[16,18,21]

As for pigmented epithelioid melanocytoma, the differential diagnosis of animal-type melanoma includes other

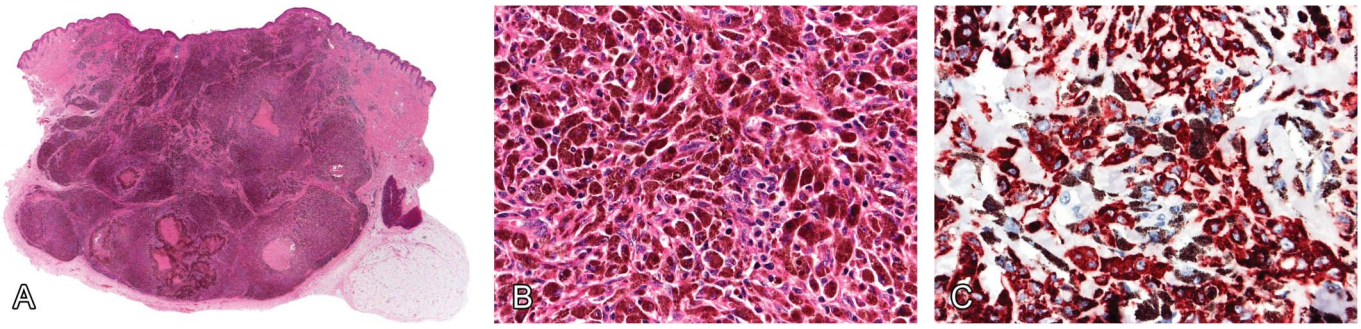

FIGURE 2. "Animal-type" melanoma (pigment-synthesizing melanoma). A, Thick, nodular melanoma with heavy pigmentation and numerous necrotic areas; (B) detail of pigmented neoplastic cells admixed with melanophages; and (C) staining for Melan-A confirms that most of the cells are melanocytes.

pigment-rich melanocytic tumors such as deep penetrating nevus and the family of blue nevi.[14–16,19] Overall, architecture of the lesion, degree of pigmentation, and cytomorphological features usually allow for a precise diagnosis.[18] Immunohistochemical markers may be used to highlight the neoplastic population of melanocytes to distinguish animal-type melanoma from tumoral melanosis (ie, dermal nodules exclusively composed of pigment-phagocyting macrophages as result of complete regression of melanoma).[23]

BALLOON CELL MELANOMA (SEBOCYTE-LIKE MELANOMA, PSEUDOLIPOBLASTIC MELANOMA, MELANOMA WITH CLEAR CELLS, AND GRANULAR CELL MELANOMA)

Melanocytes with large, finely vacuolated cytoplasm (so-called balloon cells) have been described in both benign and malignant melanocytic lesions (Fig. 4).[8,24] By definition, the term "balloon cell melanoma" should be used only when balloon cells represent more than 50% of the tumor cell population and not in cases showing only focal clusters of such cells (Fig. 5)[24]; in rare reported cases, the entire neoplasm was composed of such cells.[8] According to Kazlouskaya et al,[25] the presence of balloon cells is the most common cytological alteration among melanocytic lesions with clear cells, followed by sebocyte-like changes; in that study, melanocytes with intermediate features between balloon and sebocyte-like cells were also observed, pointing to a spectrum of clear cell changes encompassing both of these features.[25] We believe that this variant of melanoma should also include cases with pseudolipoblastic features[26] (Fig. 4C) and rare cases with granular cell morphology ("granular cell melanoma"),[27] as they all represent variations on the theme of clear cell morphology.[8]

Balloon cell melanoma is rare, representing less than 1% of all reported cases of melanoma.[8] Clinically, no

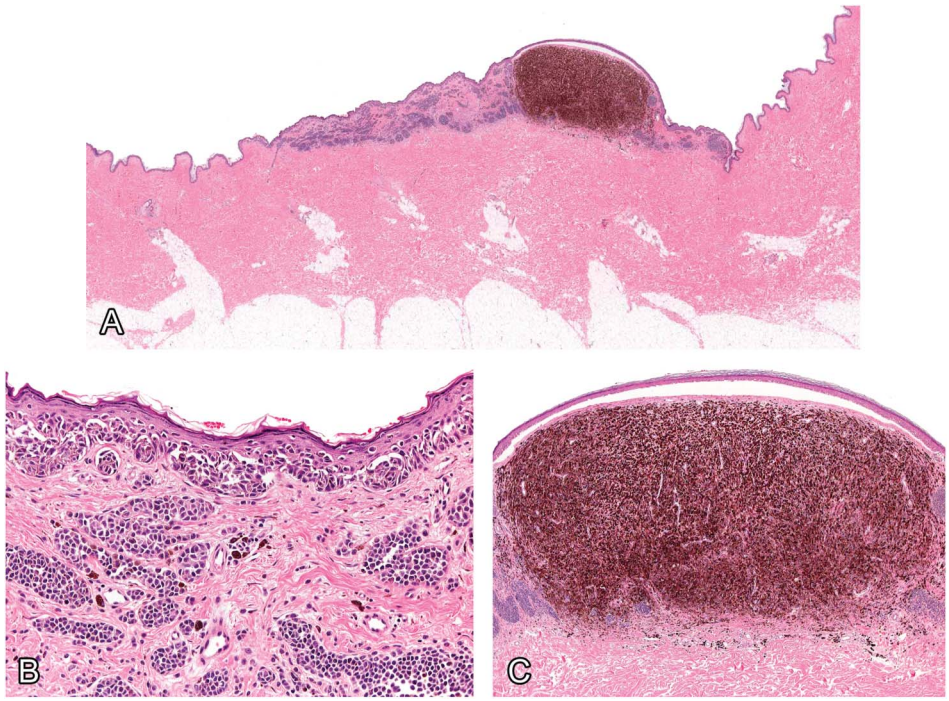

FIGURE 3. Conventional melanoma with nodular component mimicking "animal-type" melanoma. A, Asymmetrical melanocytic tumor with large, nodular, heavily pigmented component; (B) detail of the "conventional" melanoma component; and (C) detail of the pigmented, animal-type melanoma–like nodule.

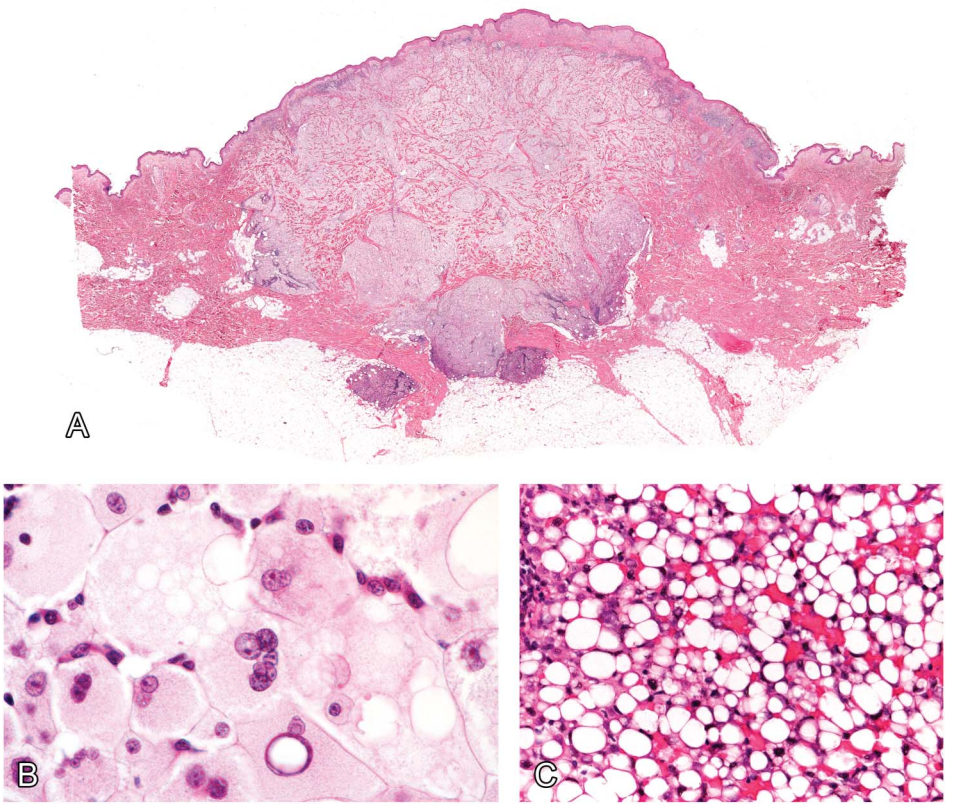

FIGURE 4. Balloon cell melanoma. A, Large, thick melanocytic tumor with the striking predominance of clear cells; (B) detail of ballooned melanocytes with ballooned, pleomorphic nuclei and clear, granular cytoplasm; and (C) lipoblast-like cells predominate in another case.

distinctive features have been reported.[28] Histopathologically, overlapping features with balloon cell nevus are not uncommon, with the presence of asymmetrical silhouette, increased mitotic index, and marked cytological atypia pointing to a diagnosis of melanoma in dubious cases.[8,25,29] However, cell pleomorphism may be only mild in balloon cell melanoma, and nuclear size may not be significantly different from that observed in balloon cell nevi.[8,25] Additional useful criteria for malignancy, if present, include the presence of necrosis and intraepidermal pagetoid spread of melanocytes.[25,30]

Differential diagnosis with nonmelanocytic clear cell neoplasms in challenging cases may rely on appropriate immunohistochemical panels featuring melanocytic markers[8]; gene expression profiling has been further proposed as a diagnostic ancillary test.[31]

BASOSQUAMOUS MELANOMA (BASOMELANOCYTIC TUMOR AND SQUAMOMELANOCYTIC TUMOR)

Composite tumors characterized by the combination of an epithelial malignant component (with features of either basal cell carcinoma or squamous cell carcinoma) and a melanocytic malignant component have been described under the terms "basomelanocytic tumor"[32] and "squamomelanocytic tumor,"[33] respectively (Figs. 6 and 7). By definition, in these entities, the 2 different neoplastic populations are intimately intermingled.[8,34,35]

In most reported cases, these neoplasms were located on the chronic sun-damaged skin of the head and neck region of elderly patients.[35] Histopathologically, atypical melanocytes are arranged in both nests and as single cells.[8,34,35] The epithelial component is more frequently a basal cell carcinoma (basomelanocytic tumor) and less commonly a squamous cell carcinoma (squamomelanocytic tumor).[35–37] As expected based on the abovementioned definition, the melanocytic population is always observed growing in close approximation to the carcinomatous component.[8,34,35]

Several theories have been proposed to explain the pathogenesis of this peculiar phenomenon.[34,35,38–40] With the caveat of a relative dearth of investigative data supporting such models, 3 of them seem to stand out as the most reasonable theories attempting to provide a framework for the occurrence of these uncommon neoplasms. According to the field cancerization theory, exposure to a common carcinogenic factor (ie, ultraviolet exposure) within a field area would predispose to the proliferation of 2 distinct clones with different phenotypic origin resulting in the development of 2 intermingled neoplasms; indeed, chronic sun exposure seems as a recurrent risk factor in reports of basomelanocytic and squamomelanocytic tumors.[34,35] The tumor divergent (collision) theory states that the 2 neoplastic populations arise independently, maintaining distinct immunohistochemical and ultrastructural phenotypes during the growth of the biphasic neoplasm.[35,39] Last, under the tumor convergent theory, the 2 phenotypically different cell populations are believed to derive from a common progenitor stem cell subsequently

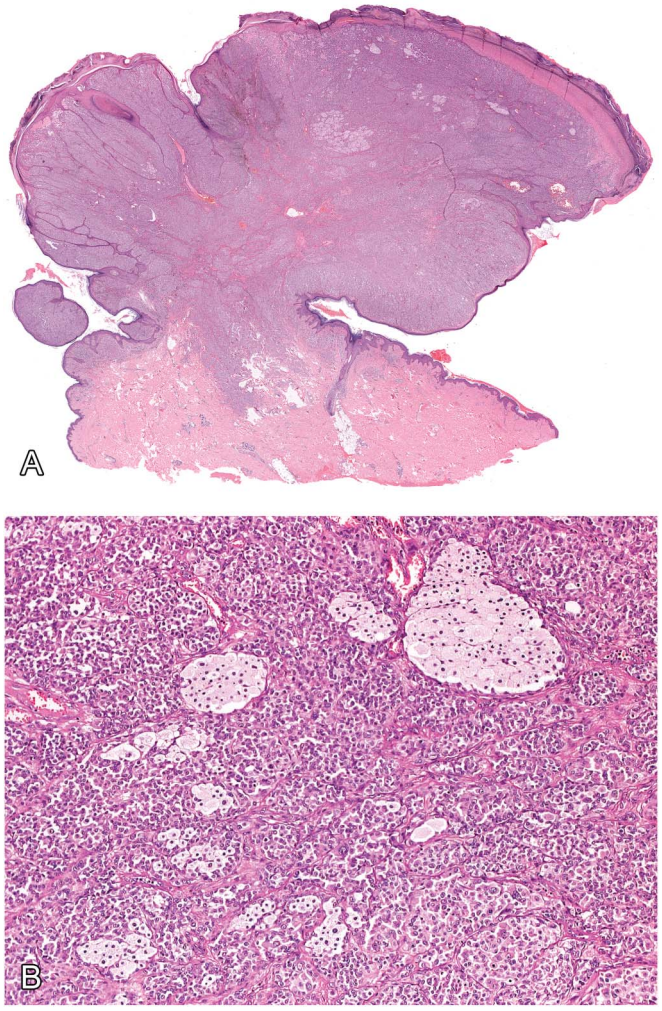

FIGURE 5. Conventional melanoma with focal balloon cells. A, Large, exophytic melanocytic tumor with focal clusters of clear cells; and (B) detail of the tumor with clusters of ballooned melanocytes.

undergoing dual differentiation, akin to what is observed in carcinosarcomas.[35] Proponents of the latter theory cite occasional reports of immunohistochemical and/or ultrastructural biphenotypia, as well as concordant genetic aberrations in basomelanocytic/squamomelanocytic tumors.[34,35,39] In our opinion, however, the tumor convergent theory in the setting of combined keratinocytic–melanocytic malignant tumors should be viewed with caution; indeed, the degree of transcriptional reprogramming needed to shift from a keratinocytic to a melanocytic phenotype (and vice versa) would be very significant, scarcely in keeping with the limited extent of malignant progression usually observed in basomelanocytic and squamomelanocytic tumors.[34,35,39] In fact, in our experience, most of these cases can be considered as a collision of 2 different, unrelated neoplasms.

Measuring Breslow's thickness in basomelanocytic and squamomelanocytic tumors is a challenging issue, and the question remains as to whether the intraepithelial melanocytic complexes intermingled within the intradermal carcinomatous component should be regarded as still in situ, or as invasive.[34,35,39] It seems reasonable, as suggested in recent literature, that only intradermal melanocytes lying outside of the carcinoma islands should be regarded as invasive, and measurement should thus be taken accordingly.[35]

Basosquamous melanomas should be differentiated from reactive, benign melanocytic hyperplasia within basal cell and squamous cell carcinoma.[34,35,39] In the latter, hyperplastic melanocytes appear as scattered bland, dendritic cells arranged as solitary units in equidistant fashion within the epithelial neoplasm, commonly sparing the basal layer.[35,39] Melanocytic hyperplasia is confined to the carcinoma, never extending to the adjacent epidermis.[34,35]

BLUE NEVUS–LIKE MELANOMA AND MELANOMA ARISING IN BLUE NEVI ("MALIGNANT BLUE NEVUS")

Malignant melanocytic tumors with histologic features reminiscent of blue nevi have been often grouped together under the umbrella term "malignant blue nevus (Fig. 8)."[41–43] In this regard, as proposed by Massi and LeBoit,[44,45] it is the authors' view that 2 distinct clinicopathological categories should be identified, namely blue nevus–like melanoma (BNLM; defined as melanoma cytologically and/or architecturally mimicking blue nevi) and melanoma arising in blue nevus (MABN; defined as melanoma associated with a preexistent benign melanocytic proliferation belonging to the blue nevus group). Accordingly, the term "malignant blue nevus" should be best avoided, including different types of melanoma and thus representing a potential source of diagnostic and therapeutic pitfall.[46]

BNLM more frequently occurs on sun-exposed areas, presenting clinically as a nodular, intensely pigmented, thick tumor.[41,44] Histopathologically, the presence of an atypical melanocytic proliferation at the dermoepidermal junction may be helpful to distinguish BNLM from MABN.[44,45] The dermal blue nevus–like areas may mimic both common and cellular blue nevi, representing the entire lesion or only part of it.[47] Histopathological features of malignancy include growth in sheets of cells with high cellularity, foci of coagulative necrosis, prominent cytological atypia, and increased mitotic rate.[43,44] Melanophages are numerous.[44]

MABN may be associated with common blue nevus, cellular blue nevus, and with any other type of dermal melanocytosis.[45,46,48,49] This variant of melanoma shows a predilection for male sex and the head and neck area.[45,48] A history of enlargement or ulceration of a dark lesion that had been present for many years is not uncommon.[48] Histologically, a diagnosis of MABN may be challenging, as clear-cut diagnostic criteria have not been described yet.[45–47] Detection of a distinctly benign component in the context of the tumor (or evidence of a previous biopsy featuring the presence of a benign component) is mandatory to formulate a diagnosis of MABN.[46] Histopathological criteria suggestive of a diagnosis of MABN include diameter of the tumor >2 cm, infiltrative borders, the presence of a population of epithelioid and spindled melanocytes with high-grade cytologic atypia arranged in nodules on the background of a blue nevus

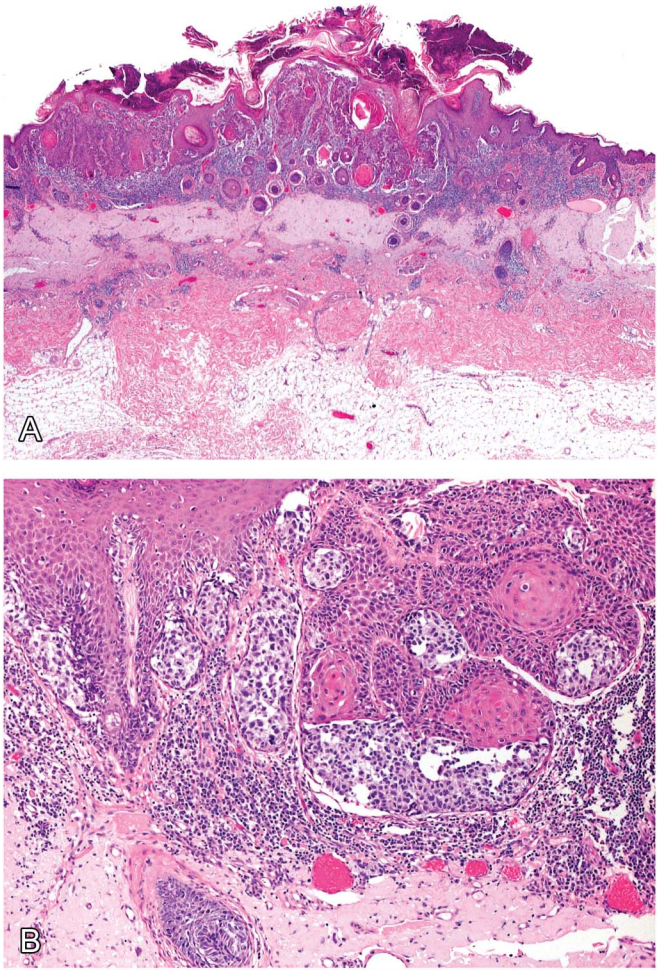

FIGURE 6. Basosquamous melanoma. A, Asymmetrical tumor with intermingled epithelial and melanocytic components; and (B) detail of the tumor showing complexes of melanoma associated with complexes of a squamous cell carcinoma.

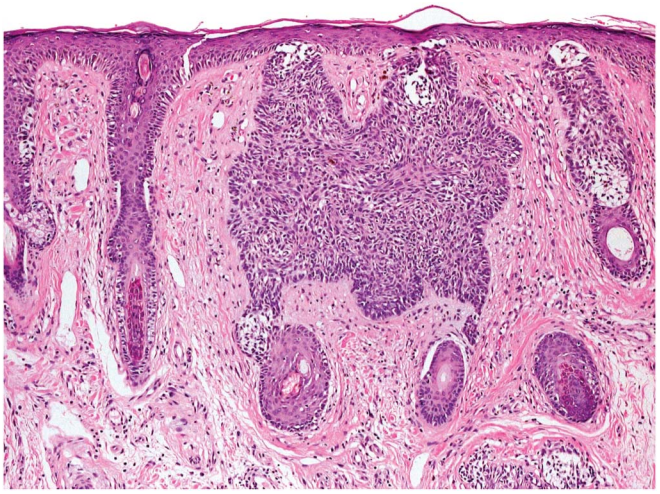

FIGURE 7. Basosquamous melanoma. Melanoma in association with a superficial basal cell carcinoma. Note the complexes of melanoma arranged also in the epithelium outside of the basal cell carcinoma.

or dermal melanocytosis, areas of coagulative tumor necrosis, and high mitotic activity (a mitotic rate of $>2/mm^2$ is considered diagnostic, with a mean of 6 mitotic figures/mm^2).[45,47,48] The transition between the benign and malignant components is usually abrupt.[45,46]

Of note, MABN appears to share a common genetic background with other melanocytic neoplasms belonging to the blue nevus family and uveal melanoma, namely lack of conventional *BRAF*/*NRAS* mutations, presence of recurring activating mutations in *GNAQ* and *GNA11*, as well as less common oncogenic mutations in *CYSLTR2* and *PLCB4*.[46] Additional recurring mutations typical of uveal melanoma, such as *SF3B1* R625 mutation and *BAP1* inactivating mutations, may also occur in some cases of MABN, appearing to specifically portend malignant behavior to blue nevus–like lesions.[46]

Because of the propensity of BNLM and MABN to develop from the onset as deep dermal or subcutaneous nodules, it has been suggested that conventional measurement of Breslow thickness may not accurately predict biologic behavior in this setting, with calculation of the largest diameter of the neoplastic nodular component appearing as a more effective parameter for prognostic purposes.[48]

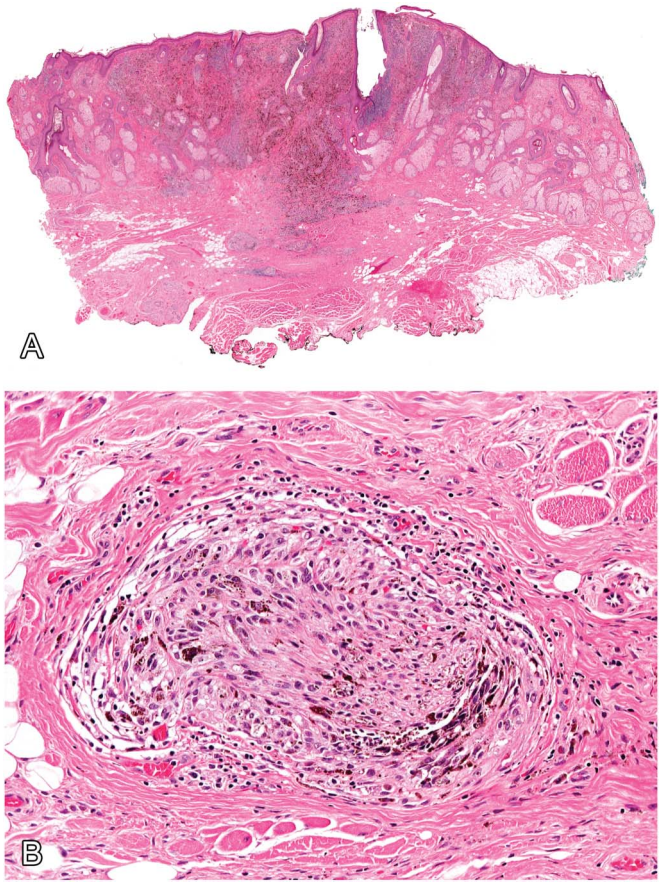

FIGURE 8. Blue nevus-like melanoma. A, Asymmetrical, pigmented melanocytic tumor. B, Detail showing epithelioid, spindled, and dendritic melanocytes.

BULLOUS/ACANTHOLYTIC MELANOMA

Bullous melanoma is an uncommon histopathological variant of melanoma characterized by extensive, confluent dyscohesion of neoplastic melanocytes in proximity of the dermal–epidermal junction (Fig. 9).[50,51] Analogous cases to those reported as bullous melanoma have been referred to as "acantholytic-like malignant melanoma"[52,53] and "dyscohesive malignant melanoma."[54] The heel and foot were anatomical sites involved in most of the reported cases, pointing to an additional role of mechanical stress in the acquisition of bullous morphology.[50] Histopathologically, bullous melanoma is defined by the development of variably large subepidermal, basilar, or suprabasilar blisters in the context of an otherwise conventional melanoma, thus not posing significant diagnostic challenges.[8,50] By contrast, measurement of the Breslow level will be affected by the vertical diameter of the blister, with the risk of overestimating tumor thickness.[50] Indeed, it seems reasonable that the thickness of the blister's cavity should not be considered in the measurement and be subtracted from the overall thickness, thus achieving a measurement better related to the actual tumor mass.[50]

Of note, a similar phenomenon of dyscohesion of malignant melanocytes may be observed in the dermal component, resulting in the histopathological picture of pseudoglandular melanoma (see below).[8,55]

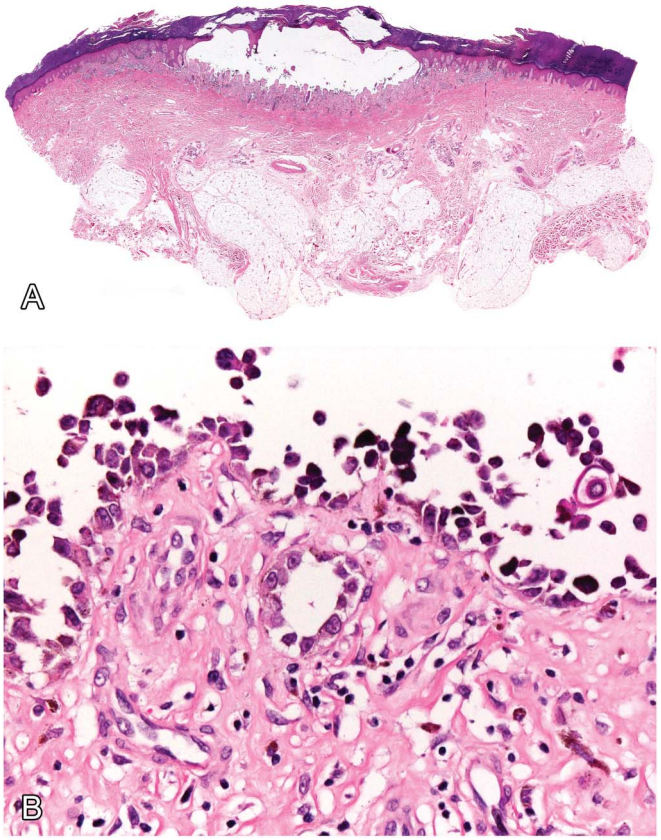

FIGURE 9. Bullous/acantholytic melanoma. A, Acral melanocytic tumor with prominent subepidermal cleft; and (B) detail of "acantholytic," pleomorphic melanocytes at the base of the bulla.

CLEAR CELL SARCOMA

Clear cell sarcoma (also known as melanoma of the soft parts) was originally described by Enzinger in 1965[56] as a deep-seated tumor with a predilection for distal tendons and aponeuroses of young adults (Fig. 10). Several cases of a superficial variant of this neoplasm have been subsequently reported, posing a significant challenge in the differential diagnosis from melanoma, with special regard to dermal melanoma, spindle cell melanoma, and metastatic melanoma.[57–59] Despite an immunophenotype consistent with melanocytic differentiation (ie, positivity for several melanocytic markers such as S100, Melan-A, HMB45, MiTF, and Sox-10), clear cell

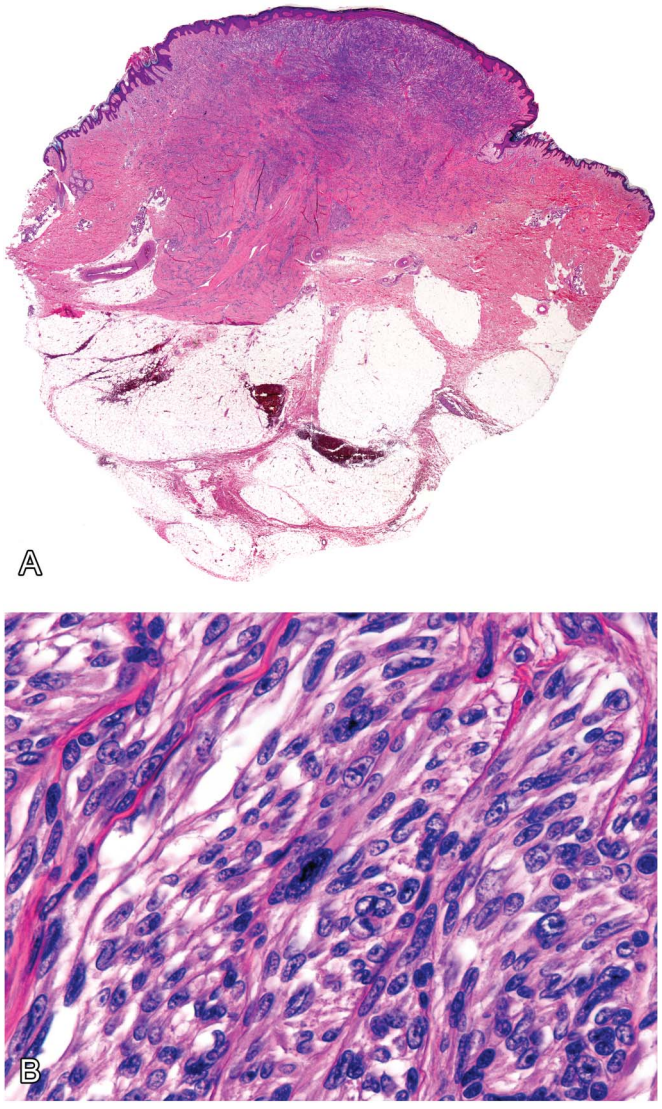

FIGURE 10. Clear cell sarcoma. A, Dermal melanocytic tumor infiltrating the subcutaneous fat and composed of (B) clear, spindled cells with pleomorphic nuclei.

sarcoma is still regarded as a tumor of uncertain lineage.[59,60] Importantly, a distinctive t(12;22) translocation is present in 70%–90% of clear cell sarcoma cases, resulting in fusion of *EWS* and *ATF-1* genes[61,62]; in addition to the diagnostic value, this genetic aberration is believed to drive the transcriptional reprogramming of an unknown precursor cell leading to the acquisition of phenotypical features of melanocytes.[61,62]

Histopathologically, cutaneous clear cell sarcoma is characterized by nests and fascicles of fusiform, epithelioid, ovoid, and, more rarely, rhabdoid cells, surrounded by a variably hyalinized stroma with intervening fibrous septa.[57,59] Detection of typical growth pattern, cytological pleomorphism of neoplastic cells albeit with only mild nuclear atypia, foci of clear cells, and overall low mitotic rate may be useful diagnostic findings.[57,58,60] Wreath-like multinucleated giant cells, mainly at the periphery of the tumor, represent an additional clue to a diagnosis of clear cell sarcoma.[59] Intracytoplasmic melanin deposition, a finding focally present in approximately 50% of clear cell sarcomas, is believed to mirror expression of melanocytic immunophenotype, adding to the diagnostic challenge.[57,58] Furthermore, a rare intraepidermal component may accompany the dermal growth, resulting in the picture of "compound" clear cell sarcoma, a deceitful simulator of Spitz nevi/tumors.[63,64]

DERMAL MELANOMA

Primary dermal melanoma is a variant of melanoma failing to show any intraepithelial component, overlying ulceration, or evidence of superficial regression/scarring (Fig. 11).[8,65,66] By definition, melanoma arising within a pre-existing melanocytic nevus, melanoma with blue nevus–like features, and clear cell sarcoma should be ruled out to make a diagnosis of dermal melanoma.[8,66] In addition, the eventuality of a cutaneous melanoma metastasis should be excluded as well, as histological features may largely overlap with those of primary dermal melanoma.[8,65,66]

The typical clinical presentation of primary dermal melanoma features a solitary nodular lesion in an elderly patient without aspects suggestive of melanoma.[8,66,67] Histopathologically, dermal melanoma presents as a well-circumscribed dermal tumor with frequent extension into the subcutis.[8] The growth pattern is predominantly solid, although nests and cords may be identified within the neoplasm.[8,65,68] To confirm a diagnosis of dermal melanoma, the lack of an intraepithelial component must be confirmed based on serial evaluation, and areas of regression, scarring, and ulceration must be absent as well.[8,66] Cytological features of neoplastic cells are characterized by marked pleomorphism, hyperchromatic nuclei, prominent nucleoli, and frequent mitoses.[8,65] Intratumoral necrosis, hemorrhage, and cystic degeneration may be also observed.[8,65]

The prognosis of reported cases of dermal melanoma seems to be more favorable compared with conventional melanoma of similar thickness.[69,70] However, the data in the literature should be interpreted with caution, keeping in mind both the risk of bias due to erroneous inclusion of melanocytic simulators of melanoma and the inconsistency regarding histologic criteria used in the selection of cases.[8] Indeed, a recent study by Sidiropoulos et al[69] pointing to a better prognosis for primary dermal melanoma actually included intradermal neoplasms with a spitzoid or blue nevus–like morphology, as well as cases associated with a pre-existing nevus, thus contravening the definition criteria for primary dermal melanoma.

DESMOPLASTIC MELANOMA

Desmoplastic melanoma is a rare variant of melanoma accounting for approximately 4% of all malignant melanocytic proliferations (Fig. 12).[71–73] Desmoplastic melanoma may be regarded as a distinctive subtype of spindle cell melanoma, being histopathologically characterized by a mainly dermal proliferation of spindled/fibroblast-like cells featuring a stromal collagen content greater than 90% of tumor mass.[74,75]

Data from genetic studies confirmed the uniqueness of desmoplastic melanoma.[76,77] Desmoplastic melanoma is currently ranked as one of the most highly mutated malignancies, being characterized by an extraordinarily heavy mutation

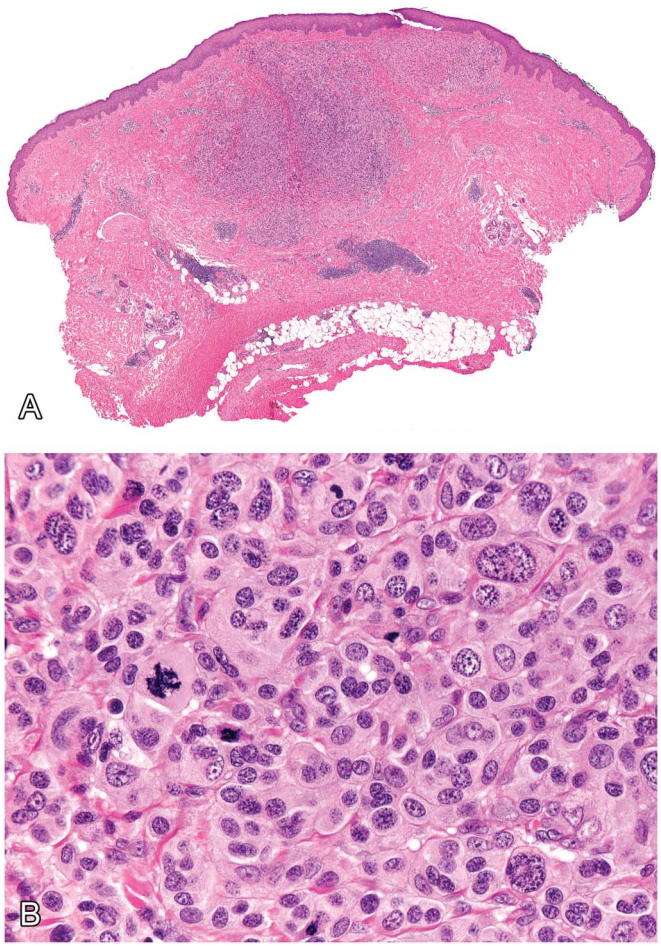

FIGURE 11. Dermal melanoma. A, Asymmetrical, dermal melanocytic tumor without connection to the epidermis and composed of (B) large, atypical, pleomorphic melanocytes. Note atypical mitoses.

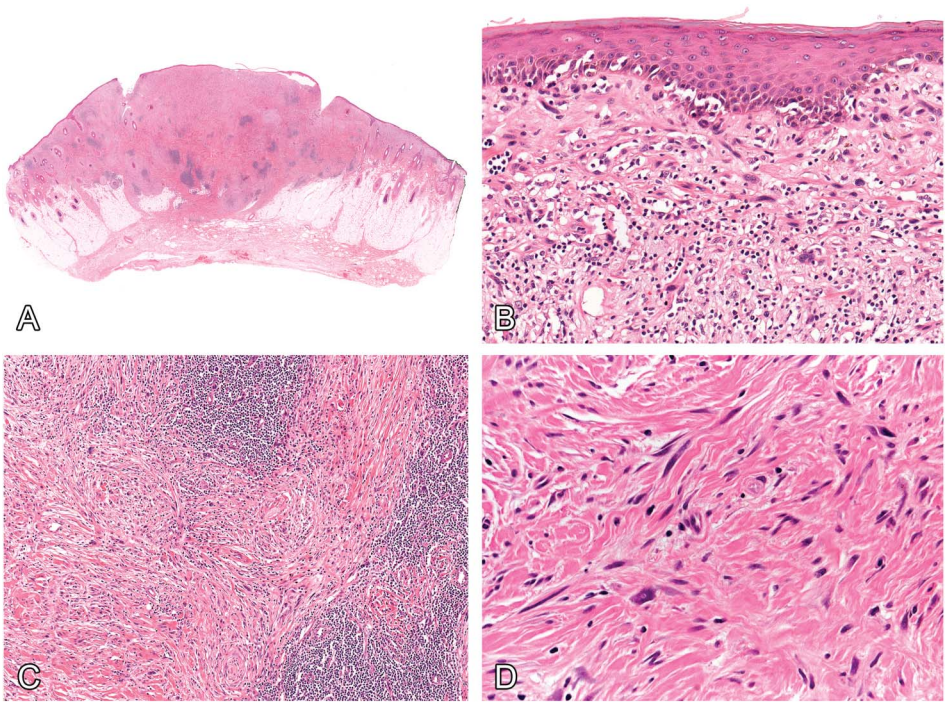

FIGURE 12. Desmoplastic melanoma. A, Asymmetrical, mainly dermal melanocytic tumor with desmoplastic stroma and patchy inflammatory reaction; (B) detail of the intraepidermal component of the tumor; (C) the dermal component is characterized by prominent, patchy inflammatory infiltrates; and (D) spindled, pleomorphic neoplastic melanocytes embedded within a desmoplastic stroma.

burden, significantly higher than other melanomas[76]; the striking frequency of cytosine-to-thymidine transitions in desmoplastic melanoma is believed to be related to a dominant mutagenic role for UV radiation, with the putative neoplastic cell of origin likely residing in the superficial dermis.[76] Most desmoplastic melanomas lack conventional oncogenic mutations in *BRAF*, *NRAS*, and *KIT*, instead harboring a significant frequency of loss of function *NF1* mutations, as well as several other genetic alterations activating the MAPK and PI3K signaling pathways.[76–78] In addition, recurrent promoter mutations in *NFKBIE* and frequent missense mutations in *TP53* were found in desmoplastic melanoma.[76]

Clinically, desmoplastic melanoma often presents with a nonspecific appearance as a deep-seated plaque/tumor neoplasm on chronically sun-damaged skin[79]; the surface is frequently amelanotic, although in some cases an overlying lentigo maligna may be evident.[74]

Neoplastic spindled cells are typically characterized by elongated and wavy shape with scant cytoplasm, inconspicuous nucleoli, and overall only focal pleomorphism.[74] A junctional, lentigo maligna–like in situ component is present in approximately 50% of cases.[74,79] Overlapping histopathological features with neuroid/neurotropic as well as myxoid melanoma may be observed, including focal Schwannian/perineurial differentiation and perineural/intraneural invasion.[74,80,81] Such findings seem to correlate with tumor thickness, increased frequency of local recurrence, and reduced disease-free survival.[71,81] A dermal patchy lymphoid infiltrate is an additional, almost invariable feature, representing a valuable diagnostic clue[74]; nevertheless, it ought to be emphasized that such finding is not entirely specific, being occasionally observed also in benign desmoplastic nevi.[82]

A nondesmoplastic (conventional) epithelioid or spindled neoplastic cell population, variably admixed with the desmoplastic component, is frequently observed in

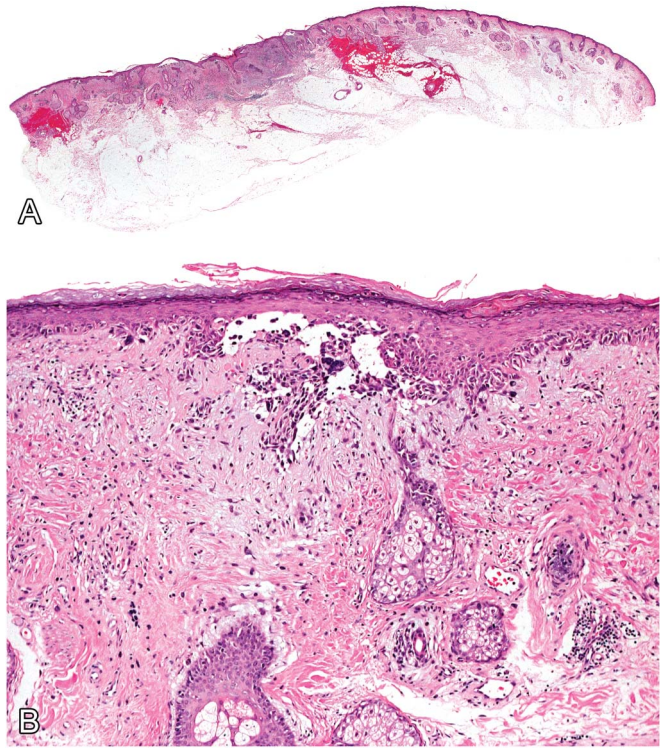

FIGURE 13. Melanoma with focal desmoplasia. A, Asymmetrical melanocytic tumor on the chronic sun-damaged skin of the head and neck area with (B) focal area of desmoplasia within the dermis.

desmoplastic melanoma.[83,84] This feature has prompted a further distinction between pure and mixed desmoplastic melanoma (Fig. 13), with the desmoplastic component greater than 90% being used as an arbitrary cutoff to define pure desmoplastic melanoma.[83,84] Such histological subclassification has prognostic and clinical value, as pure desmoplastic melanoma carries an only minimal risk of lymph node metastases, thus suggesting that sentinel node biopsy should be restricted to individuals with mixed desmoplastic melanoma.[84,85] Importantly, results from genetic studies support the rationale for this distinction, pointing to a different mutation pattern between pure and mixed desmoplastic melanoma.[86]

The differential diagnosis for desmoplastic melanoma includes fibrotic conditions, such as dermal scars, cellular fibrous histiocytoma, dermatofibrosarcoma protuberans, and fibromatosis.[87] Neoplastic cells of desmoplastic melanoma show almost invariable positivity for S100 protein, usually lacking expression of other conventional melanocytic markers, such as Melan-A, HMB45, and MiTF.[74,87] In addition, WT-1, Sox-10, nestin, and p75 are positive in most cases of desmoplastic melanoma but negative in nonmelanocytic simulators, with a sensitivity and specificity similar to S100 protein.[87]

Differentiating desmoplastic melanoma from neurofibromas may be particularly challenging, especially if only superficial biopsies are available.[88] Evaluation of CD34 staining pattern was proposed as an effective tool in this setting, but recent studies have questioned its reliability.[88,89] Nuclear expression of p53 was observed in 95% of desmoplastic melanomas but not in neurofibromas, thus representing a useful diagnostic criterion.[90]

Immunohistochemistry may also be crucial for surgical margins assessment, particularly in reexcision specimens, with the caveat that scattered S100 protein-positive nonneoplastic cells may be an occasional finding in otherwise normal scar tissue.[91]

FOLLICULAR MELANOMA

Follicular involvement by melanoma is not an uncommon occurrence, being a distinctive finding in lentigo maligna melanoma (Fig. 14).[92,93] Hantschke et al[94] first described a peculiar variant of primary cutaneous melanoma characterized by prominent involvement of the pilosebaceous unit, proposing the term "follicular melanoma." According to their definition, the depth of pilosebaceous involvement in follicular melanoma should always be greater than the length of concomitant intraepidermal growth.[94] In a recent study by Machan et al,[95] the definition of follicular melanoma was further revised by mentioning involvement of only one or a few follicles (although the upper limit was not specified). It is still unclear whether follicular melanoma derives from the clonal expansion of a melanocytic precursor cell residing within the follicular bulge, or whether it should be regarded as the result of early, prominent colonization of one or a few hair follicles by an originally epidermal melanocytic neoplasm.[92–94]

The typical clinical picture of follicular melanoma features mostly a small pigmented papule on chronically sun-damaged skin of elderly patients, resembling a comedo or an epidermoid cyst, but exceptions to this presentation have been described in the literature.[92,93,95]

An open issue in follicular melanoma is represented by the measurement of the Breslow's depth. Indeed, marked inconsistencies in reporting thickness of follicular melanoma have been described even among experienced dermatopathologists.[93] In general, perifollicular invasion in follicular melanoma has been predominantly regarded as a form of microinvasion into the adventitial dermis, thus being measured differently from the traditional vertical Breslow's depth.[92,93] In light of conflicting views in this matter, as well

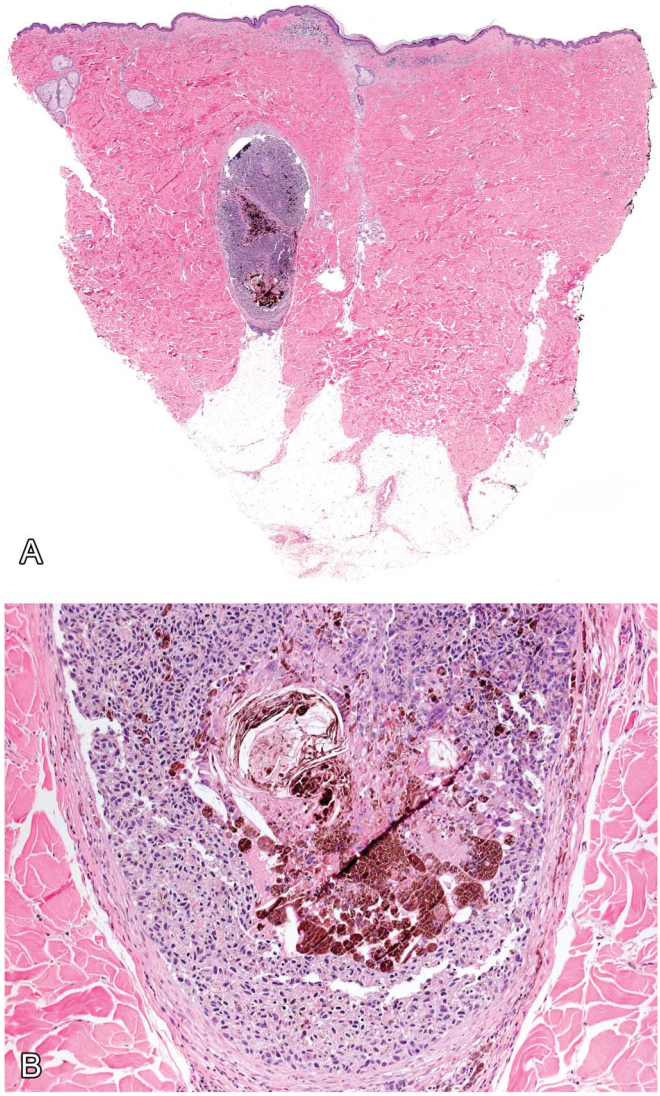

FIGURE 14. Follicular melanoma. A, Melanocytic tumor with prominent growth along one hair follicle; and (B) detail showing complete destruction of the follicle by neoplastic melanocytes. The vertical diameter along the hair follicle is much broader than the maximal horizontal diameter of the lesion.

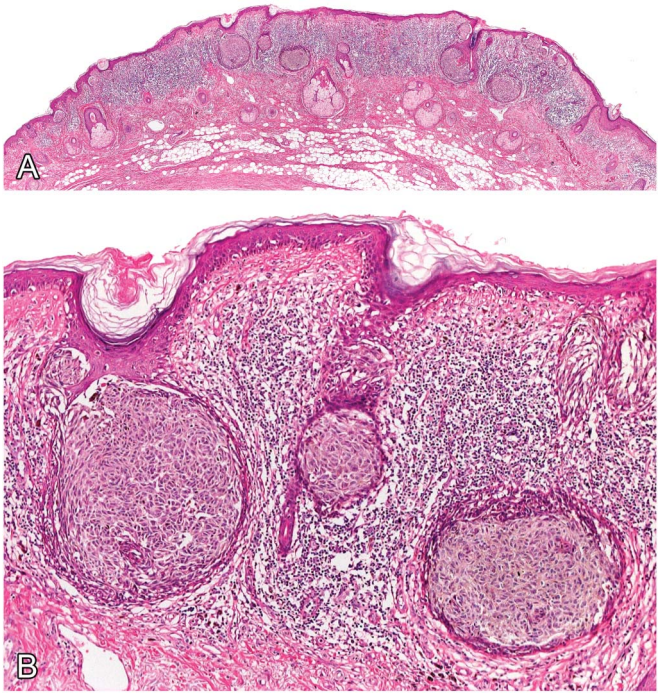

FIGURE 15. Lentigo maligna melanoma with prominent follicular involvement ("pseudo-follicular melanoma"). A, Broad melanocytic tumor with marked involvement of many hair follicles and prominent inflammation; and (B) detail of follicular involvement with very large nests of neoplastic melanocytes. Note that the horizontal diameter of the intraepidermal component is much broader than the maximal depth of the follicular involvement, unlike true follicular melanoma.

as of lack of official guidelines, it has been proposed that the final report should include both measurements, namely the traditional Breslow's depth (measured from the granular layer of the overlying epidermis to the deepest neoplastic cell in the perifollicular dermis) and the horizontal thickness of perifollicular invasion.[93] Parenthetically, it is still unclear whether the latter should be measured from the center of the hair follicle (at the hair-shaft level) or from the inner layer of the outer root sheath epithelium (resulting changes in the measurement, however, are minimal).[93]

Follicular melanoma should be differentiated from melanoma with folliculotropism (defined as invasive melanoma arising in the epidermis with extensive follicular infiltration by neoplastic melanocytes) and from melanoma in situ with follicular involvement.[93] In contrast to follicular melanoma, in melanoma with folliculotropism, the lateral extent of intraepidermal growth is greater than the depth of follicular invasion by neoplastic melanocytes (Figs. 15 and 16).[93] In addition, histopathological distinction between folliculotropic metastases of melanoma and primary follicular melanoma may be virtually impossible, because of largely overlapping histolopathological features.[96] In this context, a diagnosis of follicular melanoma should be rendered only after careful review of clinicopathological records of patients to rule out the eventuality of metastatic disease.[92,93,96]

"INVISIBLE" MELANOMA (EPITHELIOID MELANOMA IN SITU)

The term "amelanotic melanoma" has been predominantly used in the clinical context for rare lesions devoid of pigment, thus simulating several nonmelanocytic skin tumors (Fig. 17).[97] Regardless of clinical presentation (ie, as an erythematous macule, a skin-colored dermal plaque, or a papular–nodular reddish lesion), histological diagnosis of clinically amelanotic melanoma is seldom, if ever, difficult.

By contrast, on the chronic sun-damaged skin, we have not infrequently encountered cases of melanoma in situ characterized histopathologically by epithelioid, nonpigmented, intraepidermal melanocytes arranged predominantly at the dermoepidermal junction, thus prone to be misinterpreted as keratinocytes of an actinic keratosis. In the authors' experience, such phenomenon is a potential pitfall also in evaluation of margins in reexcision specimens of melanoma in situ. We believe that the term "invisible" melanoma is best used for such cases, as the denomination "amelanotic" may generate confusion with the homonymous clinical entity.

Focal parakeratosis overlying achromic melanocytes may sometimes be observed, further adding to the misleading impression of actinic keratosis. Precious diagnostic clues, if present, include focal melanin deposition in the papillary dermis, pale color of abnormal epithelioid cells at the junction and/or within suprabasal layers, and a minimal tendency to nesting. Nevertheless, final diagnosis should always rely on appropriate immunohistochemical staining.

LENTIGINOUS MELANOMA ON THE SUN-DAMAGED SKIN OF THE ELDERLY

Lentiginous melanoma on the sun-damaged skin of the elderly (LME) is a recently described variant of melanoma characterized by a broad, lentiginous growth pattern of neoplastic melanocytes within the epidermis (Fig. 18).[98] It belongs conceptually to the broad group of "nevoid melanomas" (see below),[99,100] but will be discussed separately because of its particular features. It has been suggested that LME may be regarded as the malignant end of a spectrum of junctional, lentiginous melanocytic proliferations in the elderly, including simple lentigo and atypical lentiginous junctional nevi.[101] Of note, genetic studies by fluorescence in situ hybridization corroborated the malignant nature of LME.[102] It seems reasonable that the genetic and molecular background associated with the development of LME may be closely related to that of lentigo maligna melanoma, with anatomical location (ie, trunk/limbs and face, respectively) at least partially accounting for histological differences, although further studies are needed to confirm this hypothesis.

Histopathologically, LME is characterized by bland cytology of melanocytes as well as deceitful architectural features, with a frequent lack of significant intraepidermal pagetoid spread and the predominance of melanocytes arranged in nests over those arranged as solitary units.[98,101] Indeed, high-power view of any given area in LME may be almost indistinguishable from benign lentiginous nevi.[101] By contrast, low-power evaluation of LME will reveal a key

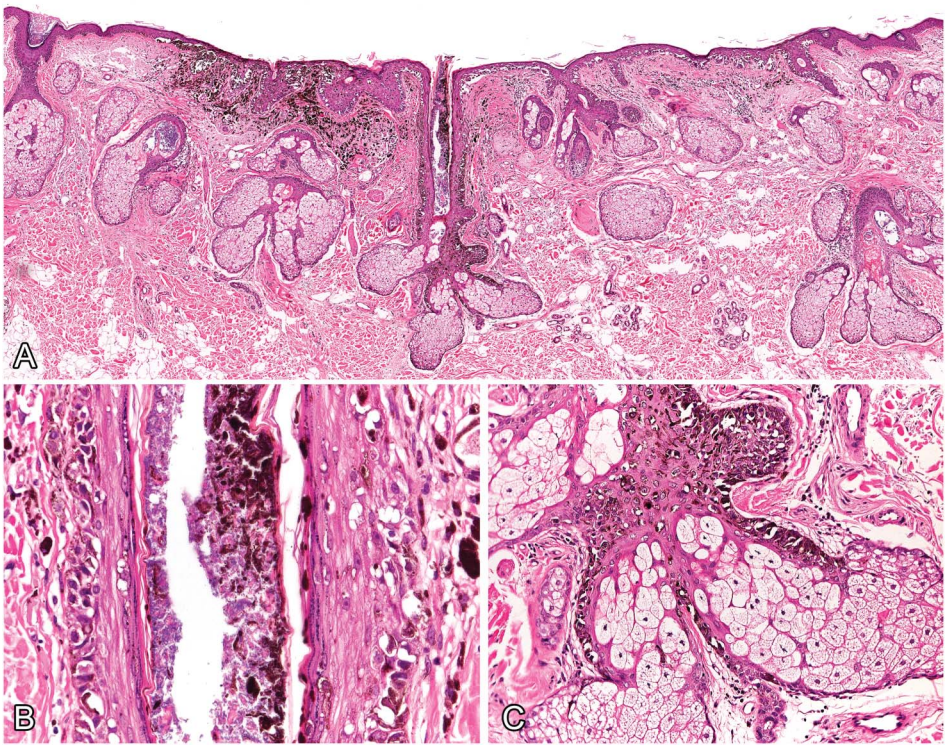

FIGURE 16. Lentigo maligna melanoma in situ with prominent follicular involvement ("pseudo-follicular melanoma"). A, Broad melanocytic tumor with marked involvement of many hair follicles; (B) detail of melanocytes within the hair follicle; and (C) detail of melanocytes within a sebaceous gland.

diagnostic clue, namely the presence of a disproportionately broad junctional melanocytic proliferation on the chronic sun-damaged skin.[98,101] In this context, it must be clearly stated that a diagnosis of LME may be very difficult or even impossible if partial biopsies are assessed without reliable clinical data regarding the lesion diameter. In fact, clinicopathological correlation is particularly helpful in cases of LME.[101]

LICHENOID KERATOSIS–LIKE MELANOMA

Although lichenoid keratosis–like melanoma (LKLM) could be conceptually included in the broad group of melanomas with regression,[23] it is the authors' view that its distinctive histopathological features deserve a separate discussion. Clinical and dermatoscopical presentation of LKLM often resembles that of lichenoid keratoses.[103] Histopathologically, LKLM is characterized by a lichenoid tissue reaction with several necrotic keratinocytes and dermal melanophages (Fig. 19).[104] The epidermis may show focal thickening of the granular layer such as in other lichenoid dermatoses. Malignant melanocytes may be just a few or completely absent in partial biopsies, and when present may be masked by the lichenoid inflammatory reaction.[104] Indeed, diagnosis in partial biopsies may be very difficult, and immunohistochemical analyses should be performed in any lichenoid keratosis that shows focal pigmentation. In this context, it should be reminded that formation of Melan-A–positive "pseudo-melanocytic nests" is a well-known phenomenon in lichenoid tissue reactions on the chronic sun-damaged skin, highlighting the need for a broad panel of melanocytic markers when assessing these lesions.[105] To further complicate the matter, the rare occurrence of

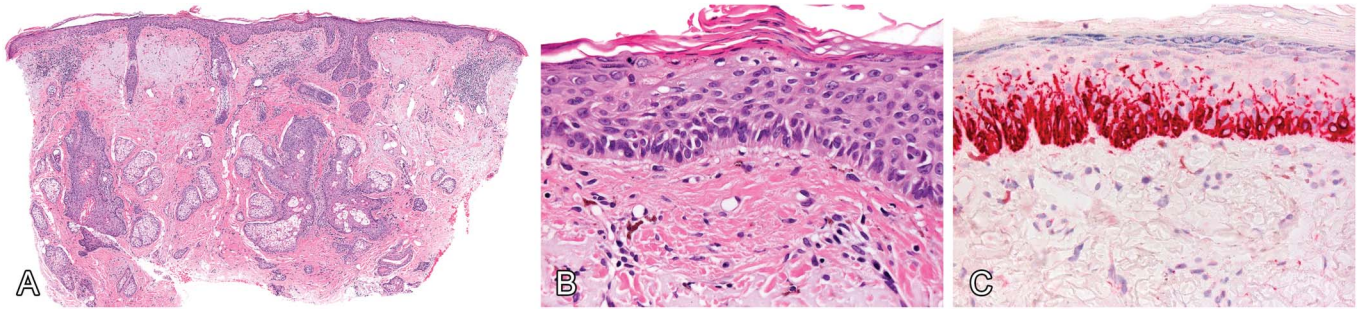

FIGURE 17. "Invisible" melanoma (epithelioid melanoma in situ). A, Punch biopsy showing minimal pigmentation and (B) the presence of epithelioid, atypical cells within the lower part of the epidermis surmounted by parakeratosis, mimicking the picture of an actinic keratosis; and (C) staining for Melan-A shows that most cells in the lower part of the epidermis are melanocytes with prominent dendrites.

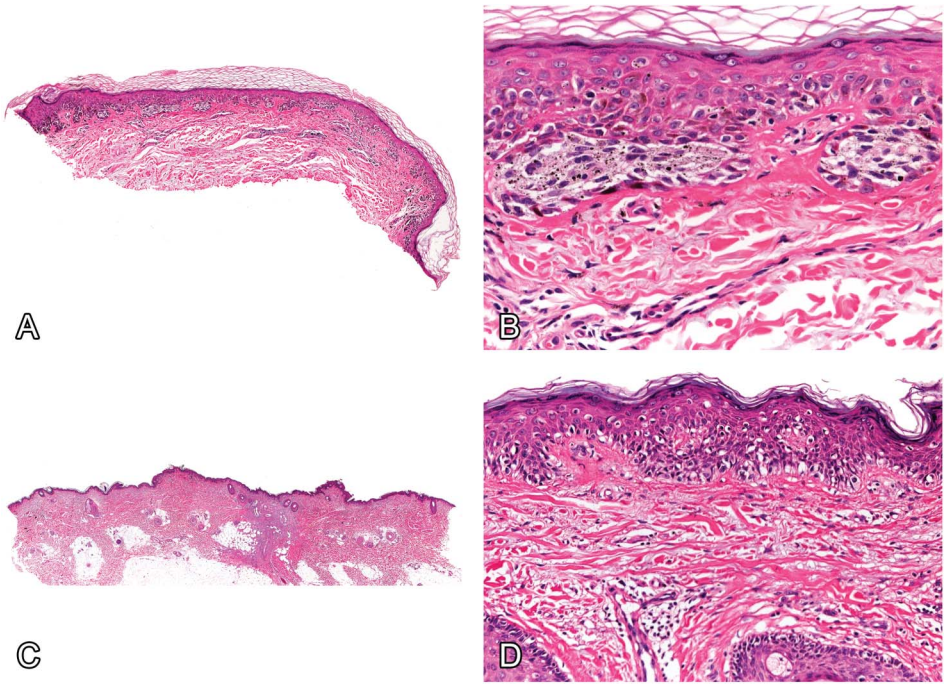

FIGURE 18. Lerntiginous melanoma of the elderly. A, Small, superficial biopsy of a melanocytic tumor on the chronic sun-damaged skin revealing (B) the predominance of nests of nevoid melanocytes arranged at the dermoepidermal junction; (C) complete excision (performed several months later) reveals a broad, junctional melanocytic tumor showing in some areas (D) the predominance of melanocytes arranged in solitary units over those arranged in nests.

seemingly true melanocytic nests arising in lichenoid inflammation (as proved by nuclear positivity for MiTF and Sox-10 among nest cells) has been recently described as well.[106] In sum, even immunohistochemistry may fail to provide indisputable results, leaving clinicopathological correlation as the ultimate criterion in challenging cases.

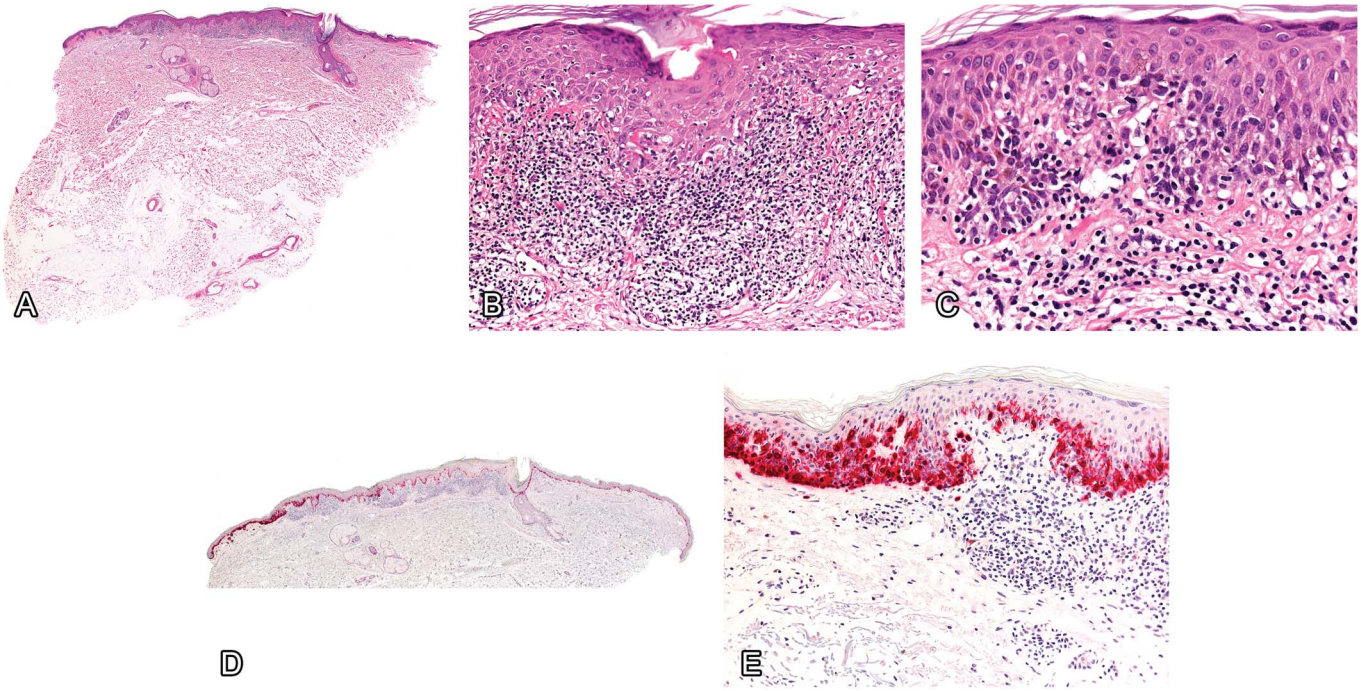

FIGURE 19. Lichenoid keratosis-like melanoma. A, Lichenoid tissue reaction showing (B) several necrotic keratinocytes and (C) focal pigmentation without increase in the number of melanocytes; (D) staining for Melan-A shows normal number of melanocytes in the epidermis above the lichenoid tissue reaction but clear increase at one edge with also superficial, small intradermal nests; and (E) detail of the edge with marked increase of intraepidermal melanocytes arranged as solitary units.

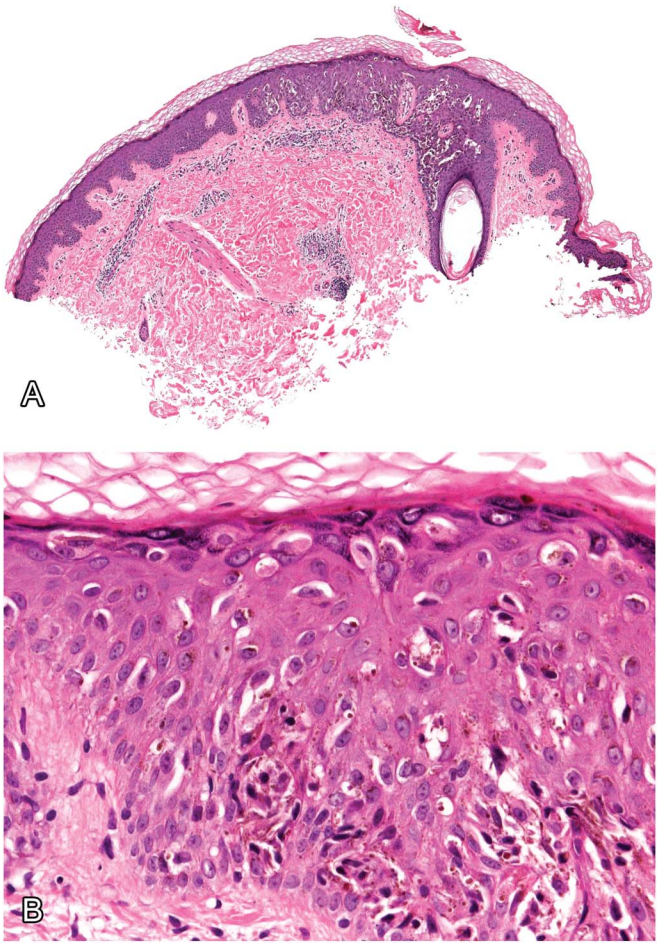

FIGURE 20. Micromelanoma. A, Intraepidermal melanocytic tumor of <2 mm of maximal diameter showing (B) conventional morphological features of melanoma in situ.

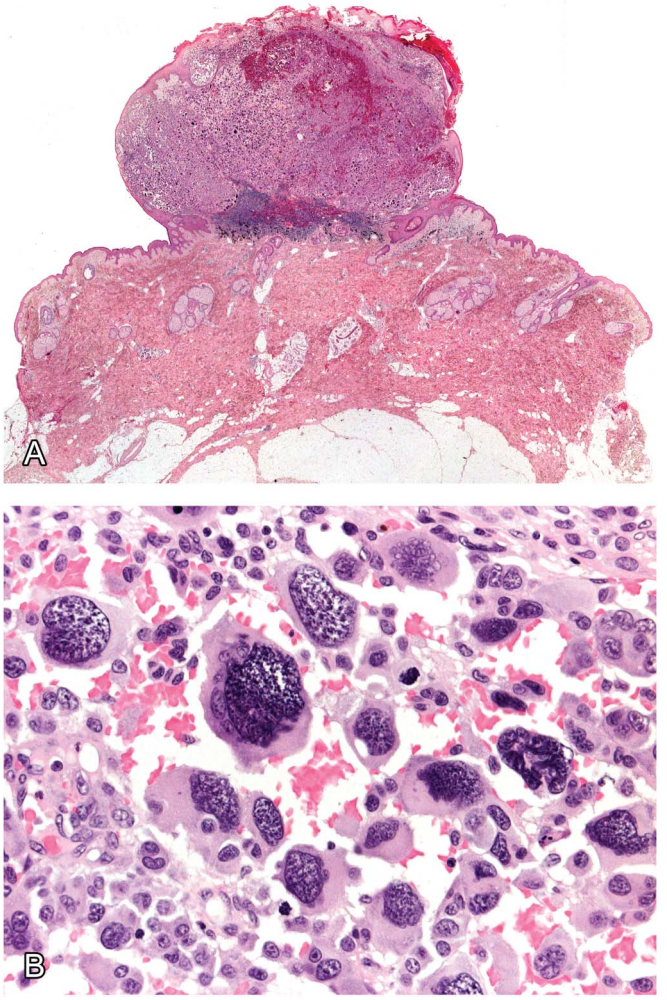

FIGURE 21. Monster cell melanoma. A, Exophytic, relatively symmetrical, ulcerated melanocytic tumor characterized by (B) the predominance of large, partly multinucleated, markedly atypical melanocytes.

MELANOMA WITH ABERRANT IMMUNOPHENOTYPE

Primary and metastatic melanoma are known to have a potential for marked phenotypic plasticity, resulting in aberrant expression of unusual lineage markers, as well as in variable loss of melanocytic markers.[8,107] Abnormal expression of nonmelanocytic markers usually represents a nonspecific phenomenon devoid of any corresponding feature at the ultrastructural level[8]; at times, however, true transdifferentiation of malignant melanocytes will be characterized by a combination of both aberrant phenotype and peculiar morphological aspects.[107]

In most cases of aberrant immunophenotype in melanoma, use of a broad panel of antibodies including highly sensitive markers such as Sox-10 will point to the melanocytic lineage.[8,107] However, a growing body of literature has recently highlighted the eventuality of very rare cases of complete undifferentiation/dedifferentiation in melanoma, either primary or metastatic.[108] In this regard, it has been emphasized that the term "undifferentiated" should be used only for cases of melanoma adopting a "vimentin-only" phenotype with loss of lineage-specific antigens, whereas dedifferentiation should imply the aberrant expression of heterologous markers (transdifferentiation, however, would seem to be a semantically more correct term).[108] Although the presence of an undifferentiated phenotype usually raises the diagnostic possibility of atypical fibroxanthoma/undifferentiated pleomorphic sarcoma, differential diagnosis in heterologous dedifferentiated lesions may include a plethora of entities, including adenocarcinoma, rhabdomyosarcoma, leiomyosarcoma, and myofibrosarcoma, among others.[8,107–111] If the undifferentiation/dedifferentiation phenomenon is observed in melanoma metastases, a history of primary cutaneous melanoma will serve as a useful anamnestic clue for diagnosis.[107,108] Furthermore, the clinical presentation of undifferentiated/dedifferentiated melanoma tumors is often inconsistent with that expected for adenocarcinoma/sarcoma.[108] It seems reasonable to hypothesize that molecular pathology will be of valuable aid in challenging cases, with undifferentiated/dedifferentiated melanoma being characterized by a constellation of oncogenic mutations and chromosomal aberrations typical of melanocytic neoplasms, but data are still lacking.[108]

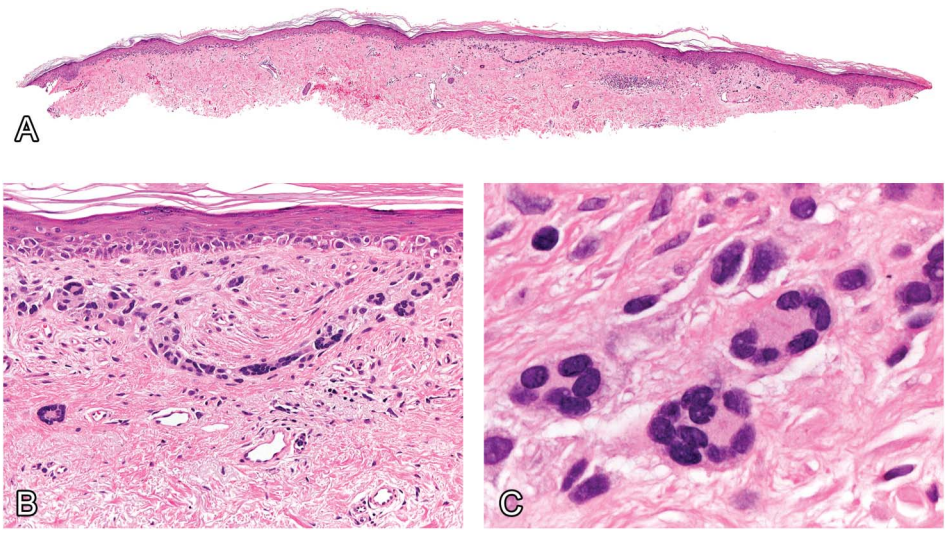

FIGURE 22. Multinucleated cell melanoma. A, Asymmetrical, broad melanocytic tumor characterized by (B) the predominance of multinucleated melanocytes with pleomorphic nuclei; (C) detail of multinucleated pleomorphic melanocytes.

MICROMELANOMA

The term "micromelanoma" refers to the clinicopathological scenario of a melanoma less than 3 mm in diameter (Fig. 20).[112,113] Micromelanoma may be viewed as a subtype within the category of "small diameter melanoma," traditionally defined as a melanoma smaller than 6 mm in diameter.[114,115] Although up to 17% of all primary cutaneous melanomas may fit within the category of small diameter melanoma,[114–116] no analogous epidemiological data on micromelanoma are available at present; according to the authors' experience, however, they seem to be exceedingly rare. Overall, micromelanoma appears to occur more frequently on the limbs of the female population.[117,118] Predictably, patients seem to be more than a decade younger than those with larger lesions at presentation.[117]

At a conceptual level, micromelanoma may be viewed as the earliest recognizable clinicopathological presentation of melanoma. A clinical diagnosis of micromelanoma may be very difficult, as application of conventional diagnostic criteria such as the ABCDE rule will likely result in missing these lesions.[119] Strict monitoring of high-risk individuals by means of digital dermatoscopy seems to be required for early clinical diagnosis.[118] Histopathologically, a combination of marked cytologic atypia and variable architectural disorder appear to be the most reliable diagnostic features, with dermal actinic elastosis, if present, further corroborating a diagnosis of micromelanoma.[116] The overwhelming majority of cases of micromelanoma are completely excised at a very early stage of disease progression,[120] and a paucity of neoplastic tissue precludes an in-depth genetic evaluation of such tumors. In this context, as molecular analyses cannot corroborate the histological impression of malignancy, the controversy concerning the classification of such lesions as micromelanomas or as benign nevi with severe atypia is still unsettled. In our opinion, however, there is no doubt that a small number of melanocytic tumors fulfill all histopathological criteria to be classified as "micromelanoma".

MONSTER CELL MELANOMA

Rare cases of primary cutaneous melanoma may present histopathologically with neoplastic melanocytes characterized by bizarre morphology, including monster, gigantic cells (Fig. 21).[8,121,122] Monster cells are usually observed in polypoid, exophytic melanoma.[8] They are characterized by a markedly increased nuclear size (up to >40 times that of normal melanocytes) with hyperchromatic nuclei and multiple nucleoli, at times forming syncytial cells.[121,122] Multinucleated melanocytes may be observed as well.[8] Monster cells are usually admixed with a majority of smaller melanocytes, but rarely represent the predominant neoplastic population.[121,122] In most cases, a diagnosis of melanoma with monster cells is straightforward, because of at least focal presence of conventional features of melanoma.[8] In doubtful cases, immunohistology is diriment.[8,121]

Cytological features of monster cells appear to mirror the presence of multiple, severe, complex copy number variations and of chromosomal instability at the genetic level, being possibly related to the more aggressive behavior frequently seen in this variant of melanoma.[123,124] On the other hand, virtually all reported cases of monster cell melanoma were thick, high-risk lesions, and at present, there are no studies demonstrating that monster cell morphology represents an independent prognostic criterion in melanoma.[123,124]

MULTINUCLEATED CELL MELANOMA

Multinucleated melanocytes with abundant cytoplasm and peripherally located nuclei can be observed in different histologic types of melanocytic nevi. By contrast, their presence in melanoma is reported to be rare, representing the majority of neoplastic cells in only exceptional cases (Fig. 22).[125,126] On the cytological level, multinucleated cells in melanoma tend to show larger nuclei and a higher degree of pleomorphism and/or hyperchromasia compared with benign nevi, although "nevoid," seemingly bland features may be observed in malignant lesions as well.[8,125,126]

Occasional case reports of melanoma with "Touton-like"[125] and "osteoclast-like"[126,127] giant cells should be regarded as morphologic variants in the group of multinucleated cell melanoma. A similar consideration applies also to cases of melanoma with a xanthogranuloma-like or atypical fibroxanthoma-like appearance.[8,128] Importantly, it should be highlighted that neoplastic cells in melanoma, including the multinucleated cell variant, may be positive for histiocytic markers such as CD68, thus posing a potential diagnostic pitfall.[125]

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CME EXAMINATION
April 2019

Please mark your answers on the ANSWER SHEET.

After participating in this activity, the physician should be better able to: 1. Analyze different types of melanocytic tumors regarding architectural, cytomorphological, and immunohistochemical features. 2. Assess the histopathological pattern of different types of melanoma with particular regard to specific variants characterized either by the presence of peculiar cell types (eg, balloon cells, multinucleated cells, signet-ring cells, etc.), by unconventional morphology (eg, follicular melanoma, bullous melanoma, small melanoma, etc.), or by stromal changes (eg, desmoplasia). 3. Distinguish between several melanoma variants with peculiar structural features and recognize challenges related to measurement of tumor thickness.

CME QUESTIONS

1. Which of the following vascular markers may be expressed by neoplastic melanocytes of melanoma?
   a. ERG
   b. CD31
   c. FLI-1
   d. Podoplanin
   e. CD34

2. Which of the following molecular features has been observed in clear cell sarcoma?
   a. t(1;5) translocation
   b. BAP loss at chromosome 3
   c. ALK fusions
   d. t(14;18) translocation
   e. t(12;22) translocation

3. Which of the following variants of melanoma requires special precautions when measuring Breslow's thickness?
   a. Angiomatoid melanoma
   b. Bullous melanoma
   c. Balloon cell melanoma
   d. Melanoma with osteoclast-like giant cells
   e. Melanoma with monster cells

4. Which of the following melanoma subtypes shares a similar genetic background with melanoma arising in blue nevi?
   a. Acral melanoma
   b. Desmoplastic melanoma
   c. Lentiginous melanoma of the elderly
   d. Mucosal melanoma
   e. Uveal melanoma

5. Which of the following antibodies is useful in the differentiation of desmoplastic melanoma from neurofibroma?
   a. p53
   b. S-100
   c. SOX-10
   d. Melan-A/MART-1
   e. HMB-45

ANSWER SHEET FOR THE AMERICAN JOURNAL OF DERMATOPHATHOLOGY
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Please answer the questions on pages 261-262 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

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Your evaluation of this CME activity will help guide future planning. Please respond to the following questions below.

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After participating in this CME activity participants should be better able to:	Pre 1 2 3 4 5	Post 1 2 3 4 5
1. Analyze different types of melanocytic tumors regarding architectural, cytomorphological, and immunohistochemical features.	O O O O O	O O O O O
2. Assess the histopathological pattern of different types of melanoma with particular regard to specific variants characterized either by the presence of peculiar cell types (eg, balloon cells, multinucleated cells, signet-ring cells, etc.), by unconventional morphology (eg, follicular melanoma,bullous melanoma, small melanoma, etc.), or by stromal changes (eg, desmoplasia).	O O O O O	O O O O O
3. Distinguish between several melanoma variants with peculiar structural features and recognize challenges related to measurement of tumor thickness.	O O O O O	O O O O O

Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 — definitely will not change, 5 — definitely will change)	1 2 3 4 5
	O O O O O

4. How many patients are likely to be impacted by what you learned from this activity?
o <20% o 20-40% o 40-60% o 60-80% o >80%

5. Please list at least one (1) change you will make to your practice as a result of this activity: _____

6. How will you apply what you learned from these activities (mark all that apply):

- o In diagnosing patients
- o In monitoring patients
- o In educating students and colleagues
- o As part of the quality or performance improvement project
- o For maintenance of board certification
- o In making treatment decisions
- o As a foundation to learn more
- o In educating patients and their caregivers
- o To confirm current practice
- o For maintenance of licensure

7. How committed are you to applying this activity to your practice in the ways you indicated above? 1 2 3 4 5
(1 —definitely will not change, 5 — definitely will change) o o o o o

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