The 2018 World Health Organization Classification of Cutaneous, Mucosal, and Uveal Melanoma

Detailed Analysis of 9 Distinct Subtypes Defined by Their Evolutionary Pathway

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• ***Context.***—**There have been major advances in the understanding of melanoma since the last revision of the World Health Organization (WHO) classification in 2006.**

Objective.—**To discuss development of the 9 distinct types of melanoma and distinguishing them by their epidemiology, clinical and histologic morphology, and genomic characteristics. Each melanoma subtype is placed at the end of an evolutionary pathway that is rooted in its respective precursor, wherever appropriate and feasible, based on currently known data. Each precursor has a variable risk of progression culminating in its fully evolved, invasive melanoma.**

Data Sources.—**This review is based on the "Melanocytic Tumours" section of the 4th edition of the *WHO Classification of Skin Tumours*, published in 2018.**

Conclusions.—**Melanomas were divided into those etiologically related to sun exposure and those that are not, as determined by their mutational signatures, anatomic site, and epidemiology. Melanomas on the sun-exposed skin were further divided by the histopathologic degree of cumulative solar damage (CSD) of the surrounding skin, into low and high CSD, on the basis of degree of associated solar elastosis. Low-CSD melanomas include superficial spreading melanomas and high-CSD melanomas incorporate lentigo maligna and desmoplastic melanomas. The "nonsolar" category includes acral melanomas, some melanomas in congenital nevi, melanomas in blue nevi, Spitz melanomas, mucosal melanomas, and uveal melanomas. The general term *melanocytoma* is proposed to encompass "intermediate" tumors that have an increased (though still low) probability of disease progression to melanoma.**

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This monograph represents a summary and discussion of a classification of melanoma that was developed for the *WHO Classification of Skin Tumours*, 4th edition, published in 2018.[1] As in other World Health Organization (WHO) "Blue Books," the classification of melanocytic tumors is based on that of melanomas because the focus of the book is on skin cancer rather than on benign lesions. It is also important to recognize the existence of benign tumors that may be related to the melanomas as potential precursors or as simulants.[2] Although many (approximately 30%–50%) melanomas arise in association with a preexisting benign putative precursor melanocytic nevus, the overwhelming majority of nevi are stable and are more likely to regress than progress to melanoma.[3] The risk of an individual nevus progressing to melanoma has been estimated to be in the order of 1 in 33 000 or less per year.[4,5] Therefore, the wholesale excision of these lesions is not recommended to potentially prevent melanoma. Indeed, individuals with large numbers of nevi are at higher risk of developing melanomas not only within nevi but also within their skin, unassociated with nevi, and hence excising nevi as a strategy

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to prevent melanoma may have limited effect and may give patients a false sense of security. Nevertheless, the recent identification of the presence of shared genomic abnormalities between melanomas and associated nevi has provided support for this precursor role of nevi.[6] The range of variation of nevi from a morphologic perspective, both clinically and histologically, and also from consideration of their genomic attributes, makes them significant as potential simulants that need to be distinguished from melanomas by reliable diagnostic techniques. Accurate diagnosis of nevi is facilitated by recognizing their biologically distinct subtypes and classifying them into the appropriate evolutionary pathway that leads to a specific melanoma subtype. Such nosology not only allows for their specific recognition but also assists in their distinction from simulants, particularly from melanoma.[7] We present here a classification based on clinical, histologic, epidemiologic, and genomic characteristics, in which 9 distinct subsets or "pathways" for the development of cutaneous, mucosal, and uveal melanomas are recognized and associated with their potential precursor and simulant lesions.

MULTIDIMENSIONAL PATHWAY CLASSIFICATION OF MELANOMA

The gold standard for melanoma diagnosis continues to be histopathology, in conjunction with clinical characteristics, despite the sometimes important contributions of immunohistochemistry (IHC), and rapid recent advances in genomic analysis of tumors. The currently used clinicopathologic classification of melanoma can be attributed to contemporaneous work by Vincent McGovern[8] in Australia and Wallace Clark[9] in the United States. These contributions led to the recognition that the vast majority of cutaneous melanomas arise from melanocytes in the epidermis and most of them evolve through 2 major stages of progression. In the first of these, the early lesions may be recognized as a pigmented patch or plaque, which expands more or less along the radii of an imperfect circle in the horizontal axis within the skin and for this reason has been termed the *radial growth phase* (RGP). In the next stage of progression, a tumor is formed that may infiltrate into the dermis or elevate the epidermis to form a nodule whose net direction of growth includes the vertical axis (below and/or above the level of the skin), so therefore termed the *vertical growth phase* (VGP). Most VGP lesions are obvious tumors; however, in the limiting case the definition of early "tumorigenic" VGP is the presence of a cluster of cells in the dermis that is larger than the largest cluster in the epidermis, or of any mitotic activity in the dermis, consistent with a lesion whose focus of proliferation is shifting from entirely within the epidermis to within the dermis as well.[10] There is evidence that "RGP only" melanomas have an excellent prognosis,[11,12] while VGP lesions have potential competence for metastasis, the likelihood of which increases with attributes that include increasing thickness, ulceration, microsatellites that currently form the basis of melanoma staging,[13] and others such as higher mitotic rate, lymphovascular invasion, and the absence of or minimal tumor-infiltrating lymphocytes.[14]

From the presence or absence of RGP and its variants, 3 major categories of melanoma were initially recognized.[15,16] One of these, termed *nodular melanoma* (NM) is a lesion that lacks a recognizable RGP but forms a tumor from its earliest recognition, and therefore has potential competence for metastasis from first diagnosis. Another variant that was recognized in the early studies was termed *superficial spreading melanoma* (SSM) by Clark et al[15] and *pagetoid melanoma* by McGovern.[16] These terms respectively recognized the major clinical property of these lesions, namely, a spreading lesion that changes over time, and a major histologic property, the presence of neoplastic cells scattered throughout the epidermis in a pattern reminiscent of Paget disease of the breast. The third major variant of melanoma was termed *lentigo maligna melanoma* (LMM),[15] also known as *melanoma arising in a Hutchinson melanotic freckle*,[16] and represents a form of melanoma that is associated with histologic evidence of severe solar damage and has a "lentiginous" rather than "pagetoid" pattern of growth within the epidermis. This lentiginous pattern of growth resembles that seen in actinic (or solar) lentigo, a lesion that occurs in skin with severe cumulative solar damage (CSD), and is characterized by melanocytic proliferation as single cells along the dermal-epidermal junction. These variants represent the major patterns of melanoma in skin that is susceptible to CSD and is exposed to sunlight, such as in populations of northern European ancestry, especially those living in sunny climates like Australia, New Zealand, and the United States, or traveling on sun-seeking vacations.[17,18]

It is the growing and changing RGP stage of melanoma that gives rise to the characteristic signs of early melanoma, described in the well-known ABCDE mnemonic.[19,20] "A" stands for "asymmetry," where one half of the lesion, for example, differs from the other half in shape or color. "B" stands for "border irregularity," whereby lesions begin to take on the morphology of an island with a highly indented coastline. "C" stands for "color variegation" whereby lesions evolve from mainly tan macules to papular/plaque lesions with a variety of colors including brown, black, and red-white-and-blue." "D" stands for "diameter," initially characterized as greater than 4 mm, although there is strictly no lower limit in the size that a melanoma can be formed. Lesions smaller than 4 mm can be diagnosed as melanoma but criteria should be stringent to avoid the phenomenon of "overdiagnosis," whereby lesions are diagnosed as melanomas that would not have ability for causing harm to the host unless they progress. Most of the histologically convincing small melanomas will be examples of NM, which are pure tumorigenic VGP lesions that can have competence for metastasis even when small and form an important exception to the ABCDE criteria.[21] "E" stands for elevation. However, not all melanomas—especially those early SSM lesions and lesions of the lentigo maligna, acral, and mucosal lentiginous types—are elevated when entirely in the in situ RGP. "E" also stands for "evolution," whereby a history of growth and other changes is often the discerning feature of the lesion. In a person with multiple atypical pigmented lesions, an evolving melanoma often presents as an "ugly duckling" sign where the lesion in question is noticeably out of step with the patient's other pigmented lesions.[22]

More recently, a theory of "divergent pathways" to melanoma formation/pathogenesis was proposed by Whiteman et al,[23] who postulated that cutaneous melanomas may arise through 2 distinct pathways, one associated with melanocyte proliferation and broadly corresponding to the SSM subtype, and the other with chronic exposure to sunlight and corresponding to LMM. Independently, genetic analyses of *BRAF*^{V600E} mutations by Maldonadoet al[24] and Curtin et al[25] indicated that they were particularly

Table 1. Classification of Melanoma (Modified From 2018 WHO Classification)
A. Melanomas typically associated with CSD
Pathway I. Superficial spreading melanoma/low-CSD melanoma
Pathway II. Lentigo maligna melanoma/high-CSD melanoma
Pathway III. Desmoplastic melanoma
B. Melanomas not consistently associated with cumulative solar damage (no CSD)
Pathway IV. Spitz melanomas
Pathway V. Acral melanoma
Pathway VI. Mucosal melanomas
Pathway VII. Melanomas arising in congenital nevi
Pathway VIII. Melanomas arising in blue nevi
Pathway IX. Uveal melanoma (not considered further in this review)
C. Nodular melanoma (may occur in any or most of the pathways)

Abbreviation: CSD, cumulative solar damage.

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common in melanomas on sun-exposed skin with little solar elastosis but comparatively infrequent in those arising in skin with marked solar elastosis. These observations thus laid the groundwork for a classification of melanoma that encompasses not only histologic but also clinical, epidemiologic, and genetic characteristics. Subsequently, it has become realized that other genomic aspects of melanoma also correlate with different pathways,[7] and together with epidemiologic, clinical and histopathologic features, allow for the distinction of 9 pathways of melanoma (including uveal melanoma, which is not further discussed here). This classification is presented in Table 1. Similar to other tumors, the patterns of genetic alterations in melanomas and their respective precursor lesions indicate that the neoplastic proliferation is initiated by gain-of-function mutations of growth-promoting genes. This can occur through point mutations, gene fusions, and gene amplification. These alterations are typically followed by loss of suppressor function through inactivating mutations, deletions, or epigenetic silencing and are followed by activation of additional growth and survival-related genes.[6] Examples of common driver oncogenes, which are characteristically mutually exclusive in any given primary tumor, include mutations of *BRAF* or *NRAS* in cutaneous melanomas and others, to be discussed in additional pathways in sections following.[6] Examples of driver fusion genes include fusions of the kinase domains of *ALK*, *ROS*, *NTRK*, *MET*, *RET*, *PRKCA*, *MAP3K8*, *BRAF*, and others, with a variety of 5′ partner genes, which occur also in a mutually exclusive pattern of each other and other oncogenic driver mutations.[26–30] In more advanced melanomas the mutually exclusive pattern of these mutations can change, as several driver mutations can exist in subclones, which can become selected out, especially under systemic therapy targeting signaling pathway components.

Kinase fusions occur predominantly in clinically benign but morphologically atypical lesions termed *Spitz tumors* but also in some non-Spitz melanomas.[31] Examples of genetic changes that promote disease progression and may be identified in melanomas include homozygous loss of *CDKN2A*, which encodes p16; inactivating mutations of *CDKN2A* (or other functional defects in the p16 protein or its expression, or in its pathway), of *TP53*, *NF1*, and other suppressor genes; and activation of various other pathways such as telomerase (often through *TERT* promoter mutations). These genetic events are characteristically associated with corresponding lesional changes that herald progression from precursor lesions (wholly benign and intermediate) to in situ and subsequently invasive melanomas, and also from invasive RGP to VGP, and continuing in metastases.[6]

Benign tumors of melanocytes are very common, generally termed *melanocytic nevi*, or often simply *nevi*. Although the term *nevus* reflects an old idea that these lesions are hamartomas, it continues to be used despite recent convincing evidence that nevi are benign neoplasms, having mutations or fusions of the same single driver oncogenes that also occur in melanomas, but are generally lacking the additional progression-related genomic changes.[6] There is also an "intermediate" category of lesions that have 1 or a few of these progression-related genomic changes (such as hemizygous loss of *CDKN2A* or a *TERT* promoter mutation) but insufficient to establish the malignant clinical behavior of a melanoma.[6] Benign nevi, and particularly the intermediate lesions, may provide challenges of diagnostic differentiation from melanomas in clinical and pathology practice. These challenges often result in diagnostic uncertainty, and the classification recognizes that, in some instances, definitive classification may not always be possible. When this occurs, it may be appropriate to use descriptive terms for them, such as *intraepidermal atypical proliferation of uncertain significance* (used for in situ proliferations), *superficial atypical proliferation of uncertain significance* (used for invasive RGP-only proliferations), or *melanocytic tumor of uncertain malignant potential* (used for tumorigenic lesions), accompanied by a differential diagnosis to allow for selection of rational clinical management.[32] These terms, when used, are always written out in full.

These benign nevi along with their corresponding intermediate lesions and melanomas were placed by Bastian[7] into an "integrated taxonomy" of melanocytic tumors, within which 9 pathways of cutaneous, mucosal, and uveal melanoma development were recognized.

Nodular melanomas likely occur in several of these pathways, representing lesions in which an intraepidermal or junctional component was present in most instances, but was overrun by an early-developing VGP tumor nodule.[33] It has also been proposed that some NMs may arise from melanocytes that have lost tumor suppressor gene function first and then acquired a gain-of-function oncogenic alteration.[34] Nodular melanoma often presents as a symmetrical tumor that can be pigmented or nonpigmented. They may be relatively small in diameter despite having reached a thickness that could be associated with a high mortality rate, and they often do not exhibit the "ABCDE" clinical signs and consequently are often not recognized clinically as melanoma.[21] Histologically, NM is defined by a VGP without an adjacent RGP.[15] They tend to grow rapidly, having a high mitotic rate,[35] and may seem to be innocuous to the patient until they have reached a considerable Breslow thickness.[36] Because of these distinctive characteristics, NM is discussed in the classification as a separate clinicopathologic entity.

The pathways of cutaneous and mucosal melanoma, with inclusion of simulant and precursor lesions, and their associated genomic aberrations, are listed in Tables 2 and 3.[37]

Table 2. Classification of Melanomas and Precursor Lesions on the Basis of Epidemiologic, Clinical, Pathologic, and Genomic Attributes, Pathways I to III

Pathway	Low UV Radiation Exposure/CSD				High UV Radiation Exposure/CSD	
	I				II	III
Endpoint of pathway	Low-CSD melanoma/SSM				High-CSD melanoma/LMM	Desmoplastic melanoma
Benign neoplasms (nevi)	Nevus				? IMP	? IMP
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia/ MIS	*BAP1*-inactivated melanocytoma/ MELTUMP	Deep penetrating melanocytoma/ MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma/SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations	***BRAF* p.V600E**[b] or ***NRAS***[b]	***BRAF***[b] or ***NRAS***[b] + ***BAP1***[a]	***BRAF***[b]; ***MAP2K1***[b]; or ***NRAS***[b] + ***CTNNB1***[b] or ***APC***[a]	***BRAF***[b] + ***PRKAR1A***[a] or ***PRKCA***[c]	***NRAS***[b]; ***BRAF* (non-p.V600E)**[b]; ***KIT***[b]; or *NF1*[a]	***NF1***[a]; *ERBB2*[e]; *MAP2K1*[e]; *MAP3K1*[e]; *BRAF*[e]; *EGFR*[e]; *MET*[e]
	TERT[d]; CDKN2A[a]; *TP53*[a]; *PTEN*[a]				*TERT*[d]; *CDKN2A*[a]; *TP53*[a]; *PTEN*[a]; *RAC1*[b]	*TERT*[d]; *NFKBIE*[d]; *NRAS*[b]; *PIK3CA*[b]; *PTPN11*[b]

Abbreviations: BIN, *BAP1*-inactivated nevus; CSD, cumulative solar damage; DPN, deep penetrating nevus; IAMP, intraepidermal atypical melanocytic proliferation; IMP, intraepidermal melanocytic proliferation without atypia; LMM, lentigo maligna melanoma; low/high-CSD melanoma, melanoma in skin with a low/high degree of cumulative sun/solar damage; MELTUMP, melanocytic tumor of uncertain malignant potential; MIS, melanoma in situ; PEM, pigmented epithelioid melanocytoma; SSM, superficial spreading melanoma; UV, ultraviolet; VGP, vertical growth phase (tumorigenic and/or mitogenic melanoma).

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[a] For example, *CDKN2A*, loss-of-function mutation.
[b] For example, *BRAF*, gain-of-function mutation.
[c] For example, *PRKCA*, rearrangement.
[d] For example, *TERT*, promoter mutation.
[e] For example, *ERBB2*, amplification.

Table 3. Classification of Melanomas and Precursor Lesions on the Basis of Epidemiologic, Clinical, Pathologic, and Genomic Attributes: Pathways IV to VIII

	Low to No (or Variable/Incidental) UV Radiation Exposure/CSD				
Pathway	**IV**	**V**	**VI**	**VII**	**VIII**
Endpoint of pathway	Malignant Spitz tumor/ Spitz melanoma	Acral melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in BN
Benign neoplasms (nevi)	Spitz nevus	? Acral nevus	? Melanosis	CN	BN
Intermediate/low-grade dysplasias/ melanocytomas	Atypical Spitz tumor (melanocytoma)	IAMPUS/dysplasia	Atypical melanosis/dysplasia/ IAMPUS	Nodule in CN (melanocytoma)	(Atypical) cellular BN (melanocytoma)
Intermediate/high-grade dysplasias	STUMP/MELTUMP	Acral MIS	Mucosal MIS	MIS in CN	Atypical CBN
Malignant neoplasms	Malignant Spitz tumor/ Spitz melanoma (tumorigenic)	Acral melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue nevus (tumorigenic)
Mutations	***HRAS***[b]; ***ALK***[e]; ***ROS1***[e]; ***RET***[e]; ***NTRK1***[e]; ***NTRK3***[e]; ***BRAF***[e]; or ***MET***[e]	***KIT***[b]; ***NRAS***[b]; ***BRAF***[b]; ***HRAS***[b]; ***KRAS***[b]; ***NTRK3***[e]; ***ALK***[e]; or ***NF1***[a]	***KIT***[b]; ***NRAS***[b]; ***KRAS***[b]; or ***BRAF***[b]	***NRAS***[b]; **BRAF p.V600E**[b] (small lesions); or ***BRAF***[e]	***GNAQ***[b]; ***GNA11***[b]; or ***CYSLTR2***[b]
	CDKN2A[a]	*CDKN2A*[a]; *TERT*[f]; *CCND1*[d]; *GAB2*[d]	***NF1***[b]; *CDKN2A*[a]; *SF3B1*[a]; *CCND1*[d]; *CDK4*[d]; *MDM2*[d]		*BAP1*[a]; *EIF1AX*[c]; *SF3B1*[c]

Abbreviations: BN, blue nevus; CBN, cellular blue nevus; CN, congenital nevus; CSD, cumulative solar damage; IAMPUS, intraepidermal atypical melanocytic proliferation of uncertain significance; MELTUMP, melanocytic tumor of uncertain malignant potential; MIS, melanoma in situ; STUMP, spitzoid tumor of uncertain malignant potential; UV, ultraviolet; VGP, vertical growth phase (tumorigenic and/or mitogenic melanoma).

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Common mutations in each pathway are listed; mutations already identified in benign or borderline low lesions are shown in bold.

[a] For example, *CDDN2A*, loss-of-function mutation.
[b] For example, *BRAF*, gain-of-function mutation.
[c] For example, *SF3B1*, change-of-function mutation.
[d] For example, *CCND1*, amplification.
[e] For example, *ALK*, rearrangement.
[f] For example, *TERT*, promoter mutation.

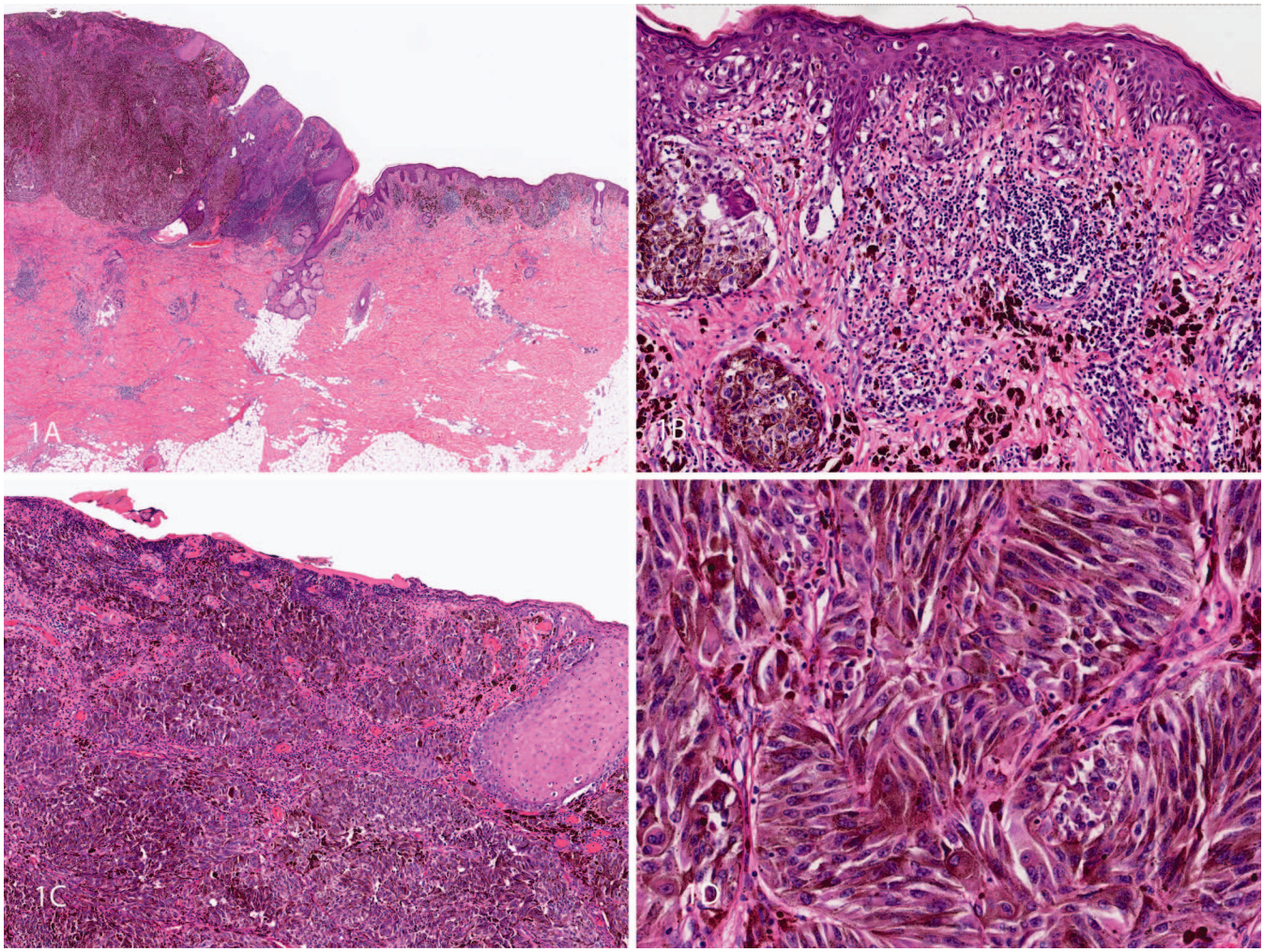

Figure 1. *Superficial spreading/low–cumulative solar damage melanoma. A, A complex lesion with a tumorigenic component in the left half of the image and a plaque component to the right, representing vertical growth phase and radial growth phase, respectively. B, In the radial growth phase, there is pagetoid scatter of uniformly atypical single melanocytes, and in addition there are quite prominent nests. There is 1 nest in the dermis that is smaller than the largest nest in the overlying epidermis. If not for the large vertical growth phase seen in (A), this could qualify the lesion as nontumorigenic invasive radial growth phase melanoma. C, The tumorigenic vertical growth phase is superficially ulcerated, as recognized by the presence of a serum crust and inflammatory reaction. D, In this example, the vertical growth phase is composed of heavily pigmented melanocytes, although pigmentation is highly variable and may be minimal or absent (hematoxylin-eosin, original magnifications ×20 [A], ×200 [B], ×50 [C], and ×400 [D]).*

Pathway I: Low-CSD Melanoma/Superficial Spreading Melanoma

The concept of classifying melanomas based on the degree of CSD of the surrounding skin is based on the observation that melanomas on sun-exposed skin with little solar elastosis have genetic alterations distinctive from those on sun-exposed skin with marked elastosis.[24,25] Most primary melanomas in the category originally termed *non–cumulative solar damage* in these genetic analyses were SSMs but other traditional melanoma subtypes such as NMs and unclassifiable melanomas were present as well. The absence of marked solar elastosis was the most powerful morphologic criterion to predict the genotype of *BRAF*^{V600E} mutation and was more reproducible among expert pathologists than the traditional designations of SSM, LMM, and NM.[38,39] Subsequently, more comprehensive genetic analyses have distinguished melanomas by anatomic site or inferred degree of cumulative sun exposure rather than the traditional McGovern-Clark categories and have confirmed the distinct patterns of genetic alterations within them.[40,41] The WHO Melanocytic Tumours Working Group decided to merge these concepts into a low-CSD category that incorporates SSM. The definition of SSM remains the same as originally proposed by Clark et al[15] and as represented in prior melanoma classifications.

Epidemiology.—This is the most common form of melanoma in Western countries and early studies of "melanoma, not otherwise classified" will have captured data mostly relevant to this subtype.[42] Following the landmark publication by Landcaster and Nelson[43] in 1957, there was gradual recognition last century that cutaneous melanomas were related to sun exposure. In a seminal study, migrants from the United Kingdom to Australia were found to acquire the higher incidence of melanoma characteristic of the Australian population, but only if they had emigrated during childhood.[44] This suggests that childhood sun exposure is crucial in establishing the risk for certain melanomas. However, there is evidence that

exposure continuing in adult life also modifies the risk.[18] In the low-CSD form of melanoma, prior cumulative sun exposure tends to be low to moderate, that is, insufficient to have caused marked solar elastosis, and typically occurs through "intermittent" exposure on weekends and on vacations. This subtype of melanoma is particularly localized to parts of the body that are exposed to the sun during these activities but not continuously throughout the typical "work week." Thus, the commonest location for melanoma in men is the back while in women it is the back of the legs or calf region (although melanomas in both sexes occur in both of these locations with lesser frequency).[45] This form of melanoma is also related to UV exposure in tanning beds, resulting in a significant though small epidemic of melanomas occurring in younger mostly female individuals.[46] Other risk factors for low-CSD melanoma established in case-control studies include the total number of nevi, large size of nevi, and clinically atypical/dysplastic nevi.[47] Correspondingly, risk factors for nevi overlap with those for melanomas. In a large case-control study, risk for melanoma was strongly related to number of small nevi, large nondysplastic nevi, and clinically dysplastic nevi. In the absence of dysplastic nevi, increased numbers of small nevi were associated with a 2-fold elevated risk, and increased numbers of both small and large nondysplastic nevi were associated with a 4-fold risk. One clinically dysplastic nevus was associated with a 2-fold risk, while 10 or more conferred a 12-fold increased risk.[48] In 2 studies, a single histologically dysplastic nevus was associated with an approximately 4-fold risk,[49,50] while lesional size greater than 4.4 mm was associated with a 5-fold risk.[51] Although hereditary nevus susceptibility genes, in addition to those associations with melanoma risk, have been described, their functional roles and contributions to melanoma risk are unclear at this time.[52]

Clinical Features.—Most of the low-CSD melanomas fall into the category that was simultaneously described by McGovern[16] as pagetoid melanoma and by Clark et al[15] as SSM, as reviewed above. These terms represent prominent histopathologic and clinical features of the lesions, respectively. Like other melanomas that begin with an RGP phase, SSMs in their earliest forms present as patches of pigmentation on the skin that evolve into elevated plaques. Although initially essentially indistinguishable from benign junctional nevi, they gradually develop the distinctive "ABCDE" clinical characteristics.[20,53]

Histopathology.—The histopathology of SSM is defined primarily by aspects of its RGP, whether or not a VGP is present. In the RGP, there is a predominantly intraepidermal proliferation of large epithelioid melanocytes, arranged along the dermal-epidermal junction and having a high propensity for forming nests. There is also scatter of neoplastic cells into the epidermis termed *pagetoid scatter* because of its resemblance to scatter of breast cancer cells into the epidermis in Paget disease of the nipple or other sites. The lesions are often heavily pigmented and quite well circumscribed (Figure 1, A through D). In the dermis, there tends to be diffuse fibroplasia and there may be areas of loss of lesional cells consistent with partial (or sometimes complete) regression in the RGP. Some degree of solar elastosis is present in most cases of SSM/low-CSD melanoma but, by definition, is mild to moderate rather than severe. Mild or grade I CSD is defined as the presence of single elastotic fibers in the dermis visible at ×20 magnification. Moderate or grade II CSD is defined as the presence of altered fibers in bunches or fascicles. In contrast, severe or grade III CSD that is characteristic of high-CSD melanomas is defined by the presence of homogeneous clumps of elastotic material that have lost their texture of individual fibrils.[54] There is often evidence of an associated nevus in SSMs, including superficial congenital pattern, common acquired, and dysplastic nevi.[55]

For practical purposes of classifying melanomas, any melanoma on nonglabrous skin with no, mild, or moderate solar elastosis should be classified as low CSD. For melanomas that arise in a background of grade III solar elastosis but show clear features of SSM such as marked pagetoid scatter, a predominance of large epithelioid melanocytes with powdery melanin pigmentation, or a contiguous melanocytic nevus as a likely precursor (as opposed to an incidental intradermal nevus as occasionally seen on the face), should also be classified as low-CSD/SSM.

Differential Diagnosis, Simulants, and Precursors.—Although at the clinical level many other entities including pigmented seborrheic keratoses and basal cell carcinomas can simulate SSM, the most relevant simulants especially at the histologic level are melanocytic nevi, which are benign tumors of melanocytes. These may also act as precursors of some melanomas; however, the vast majority of nevi are stable and will never progress—indeed, the natural history of most nevi including dysplastic nevi appears to be involution.[3] Categories of nevi in this "low CSD," predominantly *BRAF*-mutated pathway, include common acquired nevi and dysplastic nevi (Table 2). Recently, deep penetrating nevi,[56] *BAP1*-inactivated nevi,[57] and a subset of pigmented epithelioid melanocytomas[58] have been added to this category because of the presence of driver *BRAF* mutations. They represent branches of the low-CSD/SSM pathway characterized by specific secondary mutations that result in the formation of histopathologically distinctive lesions. Deep penetrating nevi often present as a combined lesion with a subset of the lesion representing a common acquired nevus. While both morphologically distinct areas harbor an identical MAP-kinase pathway mutation such as $BRAF^{V600E}$, the pigmented spindle and epithelioid cell proliferation characteristic of deep penetrating nevi has an additional mutation in the WNT pathway, most commonly an activating β-catenin mutation.[56]

In another pattern of combined nevus, there is biallelic inactivation of the tumor suppressor BAP-1, leading to a focal clone of partially transformed melanocytes presenting as a nodule of amelanotic enlarged epithelioid cells with vesicular nuclei (showing some resemblance to the cells of Spitz nevi) within a background nevus.[57] These *BAP1*-inactivated spitzoid tumors mostly occur sporadically by somatic inactivation of both *BAP1* alleles on chromosome 3. They can also occur in the setting of a cancer susceptibility syndrome, in which patients harbor a germline *BAP1* mutation and often develop multiple *BAP1*-inactivated spitzoid tumors and are predisposed to a variety of cancers, including cutaneous and uveal melanoma.

Pigmented epithelioid melanocytoma is another intermediate lesion that resembles a blue nevus but has characteristic vesicular nuclei with prominent nucleoli. It is caused by the biallelic inactivation of another suppressor gene, *PRKAR1A,* typically in a conventional nevus with a $BRAF^{V600E}$ mutation.[58,59]

Nevi with atypia, especially some dysplastic nevi, may be characterized by noncanonical *BRAF* mutations (non-

V600E),[6] or by *NRAS*[60] or other driver mutations, and by the presence of a second genomic abnormality such as a *TERT* promoter mutation, or hemizygous loss of the *CDKN2A* gene at 9p21, which codes for the tumor suppressor p16.[6]

Genomic Features.—The most commonly mutated driver oncogene in SSM/low-CSD melanoma is *BRAF*.[24,38] The most common mutation results in an amino acid substitution from a valine (V) to a glutamic acid (E) at position 600, p.V600E.[61] This was the first mutation in melanoma to be targeted with inhibitory molecules that are designed to block the active site of this protein.[62] The same mutation also occurs in most banal nevi.[6] The genomic evolution of melanoma has been studied by Zeng et al,[64] who analyzed melanomas with an adjacent nevus, melanoma in situ, or intermediate lesion. The point-mutation burden increased from benign through intermediate lesions to melanoma, with a strong UV mutation signature. Most intermediate lesions and melanomas in situ had *TERT* promoter mutations in addition to the initiating *BRAF* or *NRAS* mutation. Biallelic inactivation of *CDKN2A* marks the transition to invasive melanomas in most cases.[63,64] *PTEN* and *TP53* mutations were present only in advanced primary melanomas. Copy-number alterations emerged in intermediate and in situ lesions and continued to accumulate during progression to invasive and metastatic tumors.[63,64] Tumor heterogeneity was observed in the form of genetically distinct subpopulations as melanomas progressed.[6,63]

Pathway II: High-CSD Melanoma/Lentigo Maligna Melanoma

Epidemiology.—This form of melanoma is less common than SSM/low-CSD melanoma but its incidence has been increasing especially in very heavily sun-exposed populations including outdoor workers but also some recreational "sun worshipers." By definition, these melanomas arise in skin with severe or grade III CSD.[55]

Clinical Features.—In comparison with SSM, lentigo maligna melanoma tends to have a more poorly circumscribed border both clinically and histologically,[38] with microscopic melanoma sometimes extending a considerable distance beyond the visible clinical border. This has been associated with increased propensity for local recurrence[65] and has resulted in recommendations for LMM to be treated by excisions with wider clinical margins or comprehensive marginal evaluation such as by the Mohs technique, especially when on the face.[66] As in all of the forms of RGP melanoma, the lesions evolve from patch to plaque stages and eventually most lesions will fulfill the ABCDE criteria. Tumorigenic VGP can evolve within these lesions at any time although the pace of progression of LMM seems to be slower than that of SSM. In some cases, the VGP is desmoplastic, as will be discussed in the next section. Pigmentation is less than in SSM and some LMM lesions are almost or completely amelanotic, which can result in their initially being misdiagnosed as an inflammatory process and also contributes to the problem of margin definition.

Histopathology.—By definition, LMMs/high-CSD melanomas must demonstrate grade III solar elastosis. As in all melanomas, the characteristic histologic features are best appreciated when evaluating their RGP when this is present. The features are usually best evaluated near the periphery of the lesion because they may evolve toward a "final common pathway" of large cells with pagetoid scatter near their centers, overlapping with the pattern of SSM.[67] Severe (or moderate to severe) solar elastosis is a requirement for diagnosis of high-CSD melanoma but alone is not sufficient (occasionally low-CSD melanomas/SSMs may occur in skin with high CSD). Compared to SSM, high-CSD melanomas have less nesting and a greater tendency to lentiginous (basal) proliferation of single cells along the dermal-epidermal junction (Figure 2, A through C). This lentiginous pattern, important in diagnosis of benign as well as

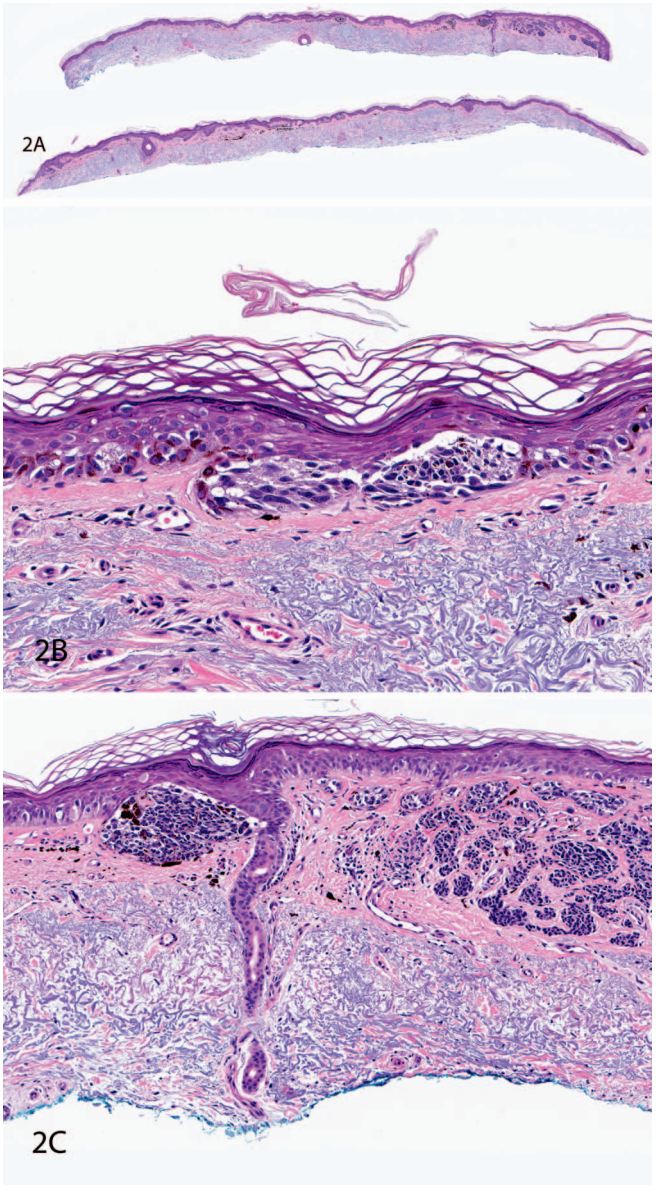

Figure 2. *Lentigo maligna/high–cumulative solar damage melanoma. A, A broad lesion occurring in skin with severe chronic solar damage (solar elastosis in which fibers have to a large extent lost their fibrillary texture with formation of homogeneous material). B, In the radial growth phase, there are single cells predominating; however, as seen in this image a few nests are characteristically present, occasionally simulating a nevus, though generally present only focally within the broad radial growth phase. C, There is an invasive component composed of somewhat nevoid melanocytes; however, these resemble the melanoma cells in the junctional component and have little evidence of maturation or dispersion at the base, as would be characteristically seen in nevus cells (hematoxylin-eosin, original magnifications ×5 [A], ×200 [B], and ×100 [C]).*

malignant melanocytic proliferations, appears to be associated with driver mutations of distinct genes, such as *NRAS* and occasionally *KIT*.[38] In contrast to solar and other lentigines, the rete ridges tend to be effaced rather than elongated, the epidermis is thinned, and the proliferation is at least focally continuous rather than intermittent. There may be a few nests near the tips and sides of elongated rete ridges, sometimes bridging between adjacent rete, in a pattern simulating a dysplastic nevus; however, in contrast to dysplastic nevi this pattern is focal within the lesion rather than symmetrically present around a central dermal nevic component, and is nonuniform across the lesion.[68] There may be apparently skipped regions, and there may be evidence of RGP regression in the form of dermal fibroplasia and absence of lesional cells in the dermis and in the epidermis. These melanomas are typically not associated with a precursor nevus in contrast to low-CSD melanomas,[69,70] and when nevus remnant cells are present the association may be incidental. Lesions that lack an RGP (ie, nodular melanomas) that occur in high-CSD skin could perhaps be classified as "high-CSD/nodular melanomas," although this was not directly addressed in the 4th edition of the *WHO Classification of Skin Tumours*.[71]

Differential Diagnosis/Simulants and Precursors.—Histopathologic differential diagnostic considerations include junctional and compound "banal" nevi and lentigines. Banal nevi are less broad than LMM, with most being less than 4 mm in diameter. Larger lesions are often dysplastic nevi, which may have cytologic atypia in addition to architectural disorder that may overlap at least focally with LMM. However, nevi in general should have a predominantly nested junctional component, with nests evenly distributed across the interface.[72] The presence of focal bridging nests should not rule out LMM.[68] A dermal component of a nevus should be centrally placed and have evidence of maturation. The dermal component of LMM may seem mature also (Figure 2, C); however, the dermal cells are not symmetrically distributed and may be multifocal, and they resemble the cells in the overlying in situ component. Lentiginous nevi may have a prominent component of single cells at the junction; the proliferation should be discontinuous and there should be less atypia than in LMM. Lesions termed *lentiginous melanoma*,[73] and *nevoid (variant of) lentigo maligna*[74] may overlap considerably with lentiginous nevi, and doubtful cases may be assigned a descriptive term such as *intraepidermal atypical proliferation of uncertain significance* or *superficial atypical proliferation of uncertain significance*, and managed according to the differential diagnosis. The diagnosis of "junctional nevus" or of "dysplastic nevus" on sun-damaged skin of the face in an older subject should be made with great caution, if at all.[75] In the case of solar lentigines, there may be almost complete overlap with LMM in situ, when there is atypia and a tendency to confluent lentiginous proliferation at the junction, and in addition, changes of a solar lentigo may be seen in contiguity with an LMM, and could cause sampling confusion.[76] It is not known whether these lesions are evolving precursors or lesions overrun by a developing in situ melanoma. Again, descriptive terminology and complete excision are appropriate forms of management.

Genomic Features.—Driver mutations differ in LMM from those in SSM and include *NF1*, $BRAF^{V600K}$, or other non-V600E mutations, *NRAS*,[38] and to a lesser extent *KIT*.[7,77,78] NF1 is a classical tumor suppressor gene and inactivation of both alleles is required to drive proliferation. When intact, it catalyzes the hydrolysis of GTP by RAS family members, accelerating their transition to the off state. When *NF1* is inactivated, *RAS* stays longer in its activated state, resulting in a more sustained activation of the MAP-kinase pathway, thus driving proliferation.[41] Because of the differences in the mutation patterns, the options for targeted therapy for metastatic LMM differ from those for SSM. These melanomas have a very high mutation burden, with predominant UV signature mutations.[79] This high mutation burden may correlate with better responsiveness to checkpoint inhibitor immunotherapy.[80]

Pathway III: Desmoplastic Melanoma

Epidemiology.—Desmoplastic melanoma (DM) accounts for approximately 1% of melanomas in the United States. It most commonly arises on skin with high CSD. These may be a subtype of pathway II, at least in the high-CSD cases, but were thought to have sufficiently distinctive features to be classified independently in the 2018 classification, and are not necessarily associated with an RGP/in situ component. The desmoplastic component of these tumors presents as a spindle cell VGP with individual cells separated by collagen fibers, a "desmoplastic" pattern of growth, which is to be distinguished from cells lying in contiguity with one another. A morphologically similar desmoplastic pattern of growth may also be seen in some areas of high-CSD/LMM, and also in acral and mucosal lentiginous melanomas, which have little or no CSD.

Clinical Features.—Desmoplastic melanoma may present as a firm scarlike tumor. The lesions are commonly amelanotic or sparsely pigmented, and the differential diagnosis of melanoma is not always apparent to the clinician.[81] In other cases, there may be a preexisting pigmented patch within which a tumor develops. The lesions are typically endophytic rather than forming a nodule.

Histopathology.—The histopathology has been recently reviewed.[82] In most cases, there is an in situ/invasive RGP component, with general characteristics of LMM. Pigment is commonly sparse or absent. In some cases, there is an inconspicuous junctional proliferation that does not meet criteria for melanoma in situ, and in a small number of cases, there is no junctional component at all.[83] These lesions were described as "nerve-centered dermal DM,"[84] with the suggestion that they arise from dermal nerves; however, in many instances such a connection is not readily evident. The tumors in the dermis are composed of spindle cells that may have an undulating or wavy fiber pattern reminiscent of schwannian differentiation (Figure 3, A through C). "Pure" and "mixed" forms of DM have been described.[85] In the pure component, the lesional cells are individually separated by delicate collagen fibers, which appear to have been synthesized by the tumor. In the mixed tumors, there is a component where the cells lie in contiguity with one another, which is an epithelial pattern of growth. In the mixed or epithelial areas, there may be mitoses and pigment may be present; however, these are generally absent in the pure DM components. The desmoplastic component is typically highly infiltrative and will extend down the septa of the panniculus in a subtle pattern that may involve specimen margins in an inconspicuous manner. A characteristic feature is the presence of nodular clusters of lymphocytes, which may correlate with the high mutation burden expressed in these tumors.[86] By

IHC, the cells of the "pure" component of DM are reactive with antibodies against pS100 and Sox10 but not with the more specific melanocytic markers such as HMB-45 and Melan-A/Mart1.[87] However, in "mixed" DM, which has an epithelioid as well as a desmoplastic component and has a worse prognosis, there may be staining of the epithelioid component with these markers and also staining of the in situ component.

Differential Diagnosis/Simulants and Precursors.—Simulants of DM include low-grade spindle cell tumors and reactive conditions. A subset of nevi, called *desmoplastic nevi*, has a delicate fibrous stroma that can resemble that of DM.[88] Many of these nevi are composed of large spindle and/or epithelioid cells with amphophilic hyaline cytoplasm and large ovoid nuclei with regular nuclear membranes, pale uniform chromatin, and prominent nucleoli. These could be regarded as atypical cells; however, these are spitzoid attributes and not characteristic of DM, and these lesions have been regarded as desmoplastic Spitz nevi, though genomic corroboration of this assignment is lacking, and this category has also been regarded as a distinct entity.[89] Other desmoplastic nevi may be composed of smaller nevoid melanocytes, lacking atypia and mitotic activity, embedded in fibrotic stroma. Some of these may be neurotized nevi, which may simulate DM.[90] However, DMs may also lack or only subtly express atypia and mitotic activity. Desmoplastic melanomas generally extend deeper than desmoplastic nevi, although superficial examples of DM may occur. The presence of nodular clusters of lymphocytes is characteristic of DMs but not of nevi. If an in situ component of a melanoma is present, usually of the lentigo maligna type (or of another lentiginous melanoma), the diagnosis of DM would be strongly favored. Reactivity for Melan-A and HMB-45 is most unusual in the desmoplastic component of DM (though not the epithelioid components of mixed DM), and this would strongly favor a nevus.[88] Low-grade spindle cell proliferations such as atypical leiomyomatous tumor/leiomyosarcoma, dermatofibroma, and dermatofibrosarcoma protuberans may sometimes raise the differential diagnosis of DM, and can be distinguished by their specific morphology aided if necessary by IHC.[71,91] Neurofibromas may express the same IHC markers as DM and have to be distinguished by consideration of the morphologic features reviewed above.[92] Finally, mature and hyperplastic scars may be difficult to distinguish from DM, and conversely occasional examples of DM may mimic a scar. Reactivity for pS100 and Sox10 should distinguish these lesions; however, the staining of occasional cells within scars should not be overinterpreted as evidence of melanoma.[93]

Genomic Features.—High-CSD–associated DMs have an extremely high mutation burden with a very strong UV signature. Inactivating mutations of *NF1* (neurofibromin),[94] promoter mutations of *NFKBIE*, and diverse activating mutations in the MAP kinase pathway are observed.[95] As previously mentioned, when *NF1* is inactivated, *RAS* stays longer in its activated state, resulting in a more sustained activation of the MAP-kinase pathway, thus driving proliferation.[41] Oncogenic mutations commonly found in other melanomas, in particular canonical mutations in *BRAF* and *NRAS*, are generally absent. Other genetic alterations known to activate the MAPK and PI3K signaling cascades have been identified, affecting *NF1*, *CBL*, *ERBB2*, *MAP2K1*, *MAP3K1*, *BRAF*, *EGFR*, *PTPN11*, *MET*, *RAC1*, *SOS2*, *NRAS*, and *PIK3CA*. These are not necessarily mutually exclusive. Some are candidates for targeted therapies.[95]

These genomic features are quite distinctive and likely reflect a form of melanoma that evolves by the slow accumulation of weakly oncogenic mutations, an evolutionary trajectory distinct from that of most other melanoma subtypes, which begin with initiating mutations in strong oncogenes such as *BRAF* and *NRAS*.[95]

Pathway IV: Spitz Melanoma

Definition and Epidemiology.—In the past, melanomas have been classified as spitzoid on the basis of cytomorphologic features such as a predominance of large epithelioid cells. However, genomic analyses have revealed that most cases with such morphologic features have genomic characteristics of low-CSD melanomas, with frequent $BRAF^{V600E}$ mutations.[96] In the revised WHO classification, we defined Spitz melanoma (SM) as the malignant counterpart of Spitz nevi (SN), defined morphologically and genomically. The spectrum from SN to SM is morphologically characterized by distinctive large spindle and/or epithelioid melanocytes and genetically by a different set of driver mutations that include *HRAS*, and fusion kinases involving *ALK*, *ROS1*, *NTRK1*, *NTRK3*, *MET*, *RET*, *BRAF*, and *MAP3K8*.[30,97] Lesions with intermediate genetic and/or histopathologic characteristics are termed *atypical Spitz tumors* (ASTs). Spitz nevi occur most commonly in childhood, while ASTs and SMs are probably more common in older age groups, although conclusive data are lacking, and there may be confounding data because of the inclusion of "spitzoid melanomas," most of which are likely low-CSD melanomas, genetically and biologically. Risk factors for the development of SN and melanomas are unknown.

Clinical Features.—Lesions ultimately diagnosed as SM tend to differ from SN in being larger, sometimes ulcerated, and having a history of continuous progressive growth and change. Spitz nevi typically present as amelanotic papules or nodules, with symmetrical, well-circumscribed raised borders, and a shiny stretched epidermis covering the lesion. Occasional examples, especially in children, are ulcerated. There is typically a history of appearance and short-lived growth of the lesion, followed by a period of stability. Spitz melanoma would not be expected to undergo this cessation of growth.

The prognosis of SM is probably not accurately predictable by using prognostic attributes developed for usual melanomas. In particular sentinel node staging does not appear to be predictive of survival, even when positive. No study has reported a survival benefit for patients with AST undergoing sentinel lymph node biopsy or completion lymphadenectomy, and these procedures, although reasonable to consider in some cases, are not considered to be standard of care for AST or for SM.[98]

Histopathology.—The lesions are defined by the presence of large spindle and/or epithelioid melanocytes. In SN, these have abundant amphophilic hyaline cytoplasm and large nuclei with regular nuclear membranes, pale chromatin, and prominent nucleoli. The lesions usually have a junctional component composed of nests of these spitzoid cells, often with prominent clefting artifact with adjacent keratinocytes that are often hyperplastic. Globoid eosinophilic "Kamino bodies" are characteristically present at the interface.[99] The cells protrude into the papillary dermis and often extend through it into the reticular dermis, having a

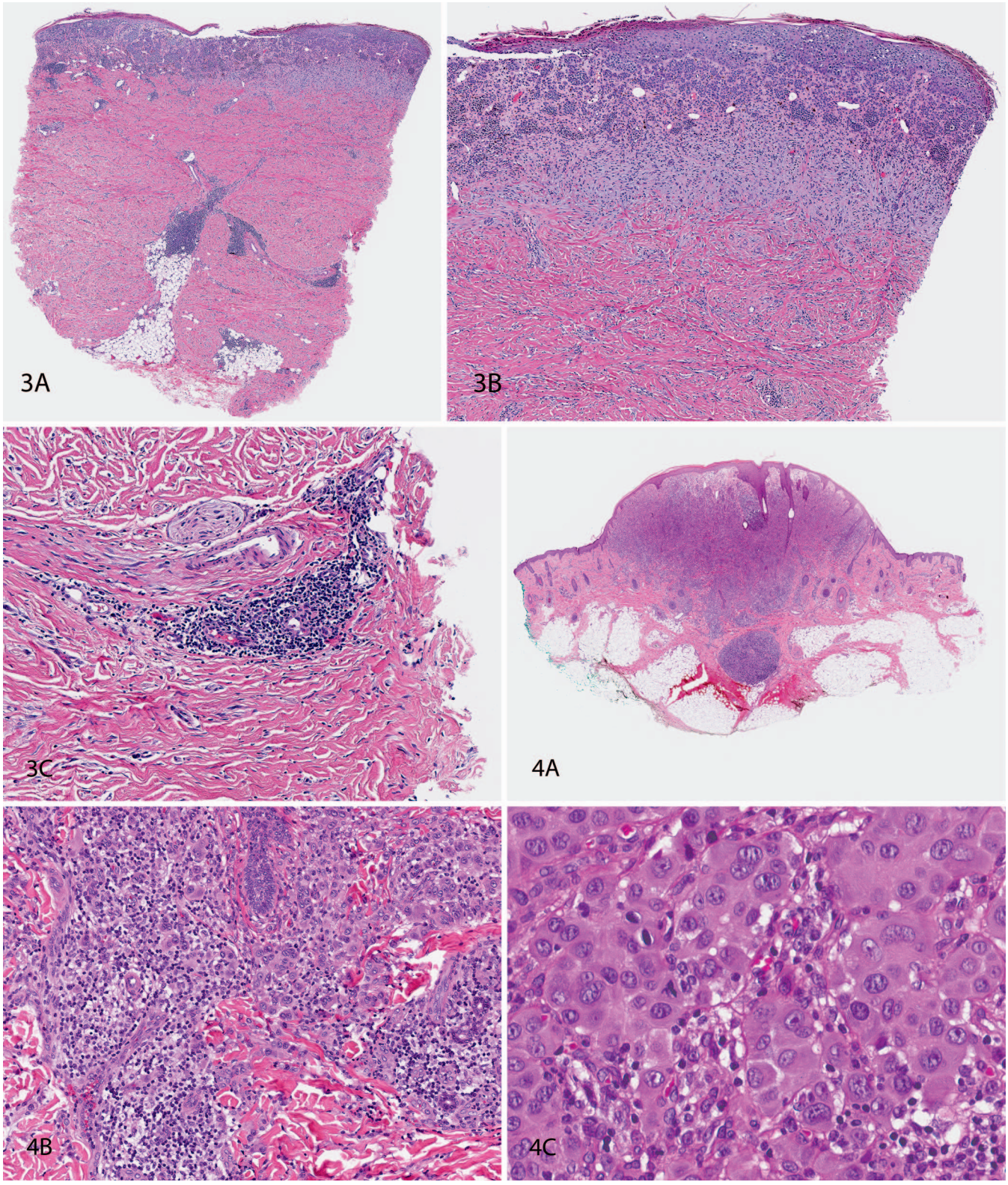

Figure 3. *Desmoplastic melanoma, high cumulative solar damage. A and B, In this punch biopsy, there is a cellular tumor in the superficial dermis; however, the architecture of the reticular dermis is subtly altered and there are prominent nodular clusters of lymphocytes, close to the presence of involvement by desmoplastic vertical growth phase (H&E, 10x and 50x). C, In this deep dermal component, there are subtle spindle cells placed between altered collagen fibers, extending to the periphery of the specimen. A nodular cluster of lymphocytes is also illustrated (hematoxylin-eosin, original magnifications ×10 [A], ×50 [B], and ×200 [C]).*

Figure 4. *Atypical Spitz tumor/Spitz melanoma. No cumulative solar damage. A, In this lesion from the scalp of a 4-year-old child, there is a tumor that extends into the deep reticular dermis with a subcutaneous "satellite" nodule. B, The tumor is composed of large epithelioid melanocytes with abundant amphophilic cytoplasm and large nuclei with generally regular nuclear membranes, pale chromatin, and prominent nucleoli. These are*

tendency to "maturation" toward a smaller cell type at the base, with dispersion of single cells into reticular dermis collagen. The diagnosis of SM is difficult, as the criteria all depend on thresholds of differences from SN that are difficult to set (Figure 4, A through C). Proposed criteria (by no means all universally accepted) include older age, large size, asymmetry, poor circumscription, ulceration,[100] and "consumption" of the epidermis,[101] failure of maturation of the dermal component,[102] increased mitotic rate with proposed thresholds for mitoses per square millimeter of fewer than 3 in adults[103] or 6 or more in children,[100] mitoses near the base,[104] and the presence of a lymphocytic infiltrate.[104,105] In a cohort follow-up study, the histologic features that most correlated with disease progression were frequent mitoses, deep mitoses, asymmetry, high-grade cytologic atypia, and ulceration.[105] By IHC, SM may exhibit loss of staining with Melan-A/Mart1, loss of stratification with irregular staining for HMB-45, high Ki-67 proliferation rate[106] (with a threshold proposed of >20% in a "hotspot"), and loss of staining for p16.[107] The latter can indicate homozygous loss of chromosome band 9p21, which has been found to be more common at the malignant end of the spectrum. This locus may be important not only because of p16, but also because it is the locus of 2 other tumor suppressors, p14 and p15, which have relevance to melanoma progression.[108] In one study, *TERT* promoter mutations were highly associated with fatal outcomes.[109] The sensitivity, specificity, and predictive value of these features and tests have in general not been tested and this is difficult because appropriate gold standards do not exist. Lesions with some of these attributes, but insufficient for a diagnosis of SM, may be classified as AST, or designated as melanocytic tumor of uncertain malignant potential, with an appropriate differential diagnosis that may be used to plan rational therapy.

In addition to IHC as discussed above, ancillary genomic testing, including comparative genomic hybridization, fluorescence in situ hybridization (FISH), and gene expression profiling can be used to contribute to establishing the diagnosis of SM. In a seminal study, Gerami et al[110] demonstrated that loss of chromosome band 9p21 (assessed by FISH) was associated with rare lethal behavior in a large group of atypical spitzoid lesions. Although these lesions were spitzoid, they had not been characterized genomically and may not have been true SM.

Imaging mass spectrometry analysis has also been proposed to differentiate SN from SM in formalin-fixed, paraffin-embedded tissue on the basis of proteomic differences.[111]

Differential Diagnosis/Simulants and Precursors.—The major differential diagnoses of SM are SN and AST. It is also important to distinguish true SMs from "spitzoid melanomas," which lack the characteristic Spitz tumor genomic profiles. These lesions with "spitzoid" morphologic characteristics mostly represent examples of low-CSD NM or from one of the other pathways. Some of them can be distinguished by use of an immunohistochemical test with the anti–BRAF V600E antibody (VE1), which, if positive, excludes an SM.[107]

The distinction between SN and SM has been discussed above. In a recent study of classical SN compared to melanomas (not necessarily spitzoid), statistically significant differences were found between SN and melanoma for the following features: pagetoid spread, atypia, maturation, elastosis, Kamino bodies, p16 expression, and the staining pattern of HMB-45. FISH testing supported the diagnosis in 36 of 37 cases.[107] This study is limited in that it did not compare ASTs with Spitz or spitzoid melanomas, which is a crucial and difficult distinction. In another study of 18 SMs, the most useful parameters for the differential diagnosis were cell density, mitoses, zonation, infiltration pattern, and consumption of the epidermis.[102]

***BAP1*-Inactivated Spitzoid Tumors.**—A subset of spitzoid lesions is associated with loss of expression of the tumor suppressor *BAP1*.[112] These tumors (now classified in the low-CSD pathway because they characteristically express the $BRAF^{V600E}$ mutant protein) are predominantly intradermal, with occasional junctional involvement. The lesional cells have varying degrees of atypia ranging from nevoid cells with minimal atypia to very large, epithelioid cells with abundant amphophilic cytoplasm and well-defined cytoplasmic borders, and vesicular nuclei with prominent nucleoli that may be pleomorphic. Some tumors have marked atypical features, including nuclear pleomorphism, high cellularity, and increased mitotic activity. These often cannot be confidently classified as benign or malignant on histologic grounds, suggesting a spectrum ranging from clearly benign to potentially malignant. The cytologic characteristics resemble those seen of cells in Spitz tumors, but the lesions lack many histologic features of SN, such as epidermal hyperplasia, hypergranulosis, clefting around junctional nests, and Kamino bodies. Some tumors have an adjacent component of smaller nevus cells, as seen in common acquired and congenital pattern nevi, and are classified as combined nevi. The lesions can be diagnosed as BAP-1 deficient by using an antibody against this antigen, which demonstrates loss of expression in the nuclei of the spitzoid cells, but not in those of the background nevi. The background lesion and the cellular nodule characteristically express the $BRAF^{V600E}$ mutation,[112] indicating that they are best placed in the "low CSD" melanoma category rather than in the category of Spitz tumor, despite morphologic overlap. These lesions can occur in the context of the *BAP1* tumor susceptibility syndrome, in which patients have already inherited an inactivating mutation of 1 *BAP1* allele and lost the remaining allele owing to a somatic event.[113] The more common "sporadic" *BAP1*-inactivated Spitz tumors have lost both *BAP1* alleles owing to somatic alterations. Counting the initiating $BRAF^{V600E}$ mutation (or other driver mutation) and the *BAP1* inactivation, these tumors thus harbor 2 (syndromic) or 3 (sporadic) somatic mutations, placing them in the "intermediate" category of tumor progression. Nevertheless, most behave in a clinically benign manner.

Genomic Features.—The genomic alterations of the various forms of Spitz tumors are distinctive, with mutually exclusive, constitutively active kinase fusions in *ROS1*, *NTRK1*, *NTRK3*, *ALK*, *BRAF*, *MET*, and *RET* genes having

←
pagetoid cytologic attributes. The mitotic rate was 4/mm², which would be a high rate in an adult but borderline in a child. C, Tumor cells do not mature or disperse well at the base of the lesion and there is an associated lymphocytic response. This lesion was classified as of uncertain malignant potential. Genomic studies were not done. In a child, its behavior will likely be benign, and no adverse effects have been reported in several years of follow-up (hematoxylin-eosin, original magnifications ×5 [A], ×200 [B], and ×400 [C]).

been identified to date.[27,28,114] Another subset of Spitz tumors has a point mutation in *HRAS*, typically accompanied by a gain of chromosome arm 11p, where *HRAS* resides.[115] *TERT* promoter mutations and loss of the chromosome 9p21 region, which contains the tumor suppressor *CDNK2A* (and also *CDNK2B*), affecting P16 and $P14^{ARF}$, or P15, respectively, have been identified in a few of the rare aggressive and occasionally lethal tumors that represent true SM[109,116,117]; however, none of these changes alone is specifically diagnostic of malignancy.[107,118,119] The BAP-1–deficient lesion has been described in the previous section.

Pathway V: Acral Melanoma

Epidemiology.—Acral melanoma (AM) refers to melanoma occurring in the glabrous, that is, non–hair-bearing skin of the volar aspects of the fingers and toes, palms and soles, and nail beds. Melanomas occurring on the dorsal aspects of these sites may represent CSD-related melanomas. Glabrous skin lacks hairs and has a thick stratum corneum, which acts as a barrier to penetration of UV into the underlying epithelium and dermis by scattering the light. Acral melanomas occur with approximately similar frequency in most ethnic groups around the world, and in populations not susceptible to CSD melanoma (such as in persons of Asian and African descent and in other populations of color); this is the most frequent subtype mainly owing to a reduced incidence of low- and high-CSD melanomas in these populations.[120] The etiology of these melanomas is unclear. UV radiation does not play a significant role and it has long been suspected that these lesions might be induced by trauma. And 2 recent independent studies[121,122] have shown that AMs commonly occur in regions of physical stress, such as flexure lines and the heel region, perhaps on the basis of repetitive motion/trauma and injury preferentially occurring at these sites. Prognosis is typically poor for AM, undoubtedly owing to a tendency for diagnosis at an advanced stage, but also perhaps to substantive differences from other subtypes.[123]

Clinical Features.—As in SSM, LMM, and other melanomas with an RGP, AMs begin with a patch lesion that enlarges more or less radially.[123–125] These lesions may form a plaque as they begin to involve the dermis and cause epidermal thickening; however, the thick stratum corneum often results in a lesion that remains flat in relation to the surrounding skin. Usual ABCDE characteristics apply in these lesions. When VGP ensues, the lesions may become ulcerated and a nodule may protrude through the ulcerated stratum corneum and form a protuberant VGP.

Histopathology.—Acral melanomas most commonly present with a lentiginous pattern of proliferation (Figure 5, A through C), and have been termed *acral lentiginous melanomas* (ALMs)[124,125]; however, pagetoid melanomas also occur in these sites. There is evidence that these pagetoid melanomas may resemble SSM genomically and likely belong to the low-CSD melanoma pathway.[126,127] The ALMs are notoriously poorly circumscribed—the last cells at the periphery of the lesions are single cells rather than nests—and there is evidence that genomic abnormalities are present in morphologically normal melanocytes beyond the periphery of the histologically recognizable RGP, constituting a "field effect."[128] This perhaps, likely in addition to compromise of therapy in order to minimize functional consequences of wide excisions, may contribute to the well-known propensity of these lesions to recur locally. The criteria for diagnosis of ALM may overlap with those of a subset of acral nevi and are discussed more extensively in the next paragraph. As mentioned above, the VGP may be composed of spindle cells with or without a desmoplastic pattern of growth, which likely differs from DM in high-CSD skin, for example, in having a lower tumor mutation burden. These melanomas are more likely to be associated with neurotropism,[129] and it is not uncommon for AMs, especially subungual ones,[130] to be seen invading into bone, perhaps because the bone is superficially located in these sites.

Differential Diagnosis/Simulants and Precursors.—The differential diagnosis of AM includes primarily acral nevi. Acral nevi are associated with ethnicity, pigmentation, age, and cutaneous melanoma risk factors including other nevi and atypical nevi.[131] In a consecutive series of 165 plantar nevi, a group of 36 distinctive nevi were designated "acral-lentiginous nevi."[132] Compared to most acral nevi, these were characterized by "elongation of rete ridges, contiguous proliferation of melanocytes at the dermoepidermal junction, presence of single scattered melanocytes, or less commonly small clusters, within the upper epidermis, poor or absent lateral circumscription, melanocytes with abundant pale cytoplasm and round to oval, sometimes hyperchromatic, nuclei and prominent: nucleoli present at the dermoepidermal junction."[132] These are features shared with many melanomas, especially subtle early lesions or changes at the periphery of established lesions. Anastomosing rete ridges, cytologic atypia, and well-formed lamellar fibroplasia as seen in dysplastic nevi were absent. Criteria that distinguish these nevi from melanoma were "lack of pagetoid lateral spread, absence of mitotic activity in the deep dermal component, and the evidence of dermal nevocytic differentiation." To these criteria we would add smaller size and greater symmetry of the nevi compared to the melanomas.

Dermoscopically, "parallel ridge" and "parallel furrow" patterns are recognized in ALM and in acral nevi, following the dermatoglyphics. The sensitivity and specificity of the parallel ridge pattern in diagnosing early acral melanoma are said to be 86% and 99%.[133,134] Histologically, if melanin granules in the cornified layer are detected as melanin columns regularly distributed under the surface furrows (which can be enhanced with Fontana-Masson staining), the lesion is "strongly suggested to be a benign acral nevus."[134] This finding depends on sectioning of the specimen perpendicular to the ridge and furrow pattern.

The genetic events in acral nevi parallel those of AMs, including frequent copy number variations,[126] differing in this regard from nevi of other sites. In a study by FISH, no abnormalities were seen in 36 acral nevi, differing from the findings in 44 AMs, for which the sensitivity of diagnosis was 88.6%.[135]

Genomic Features.—Acral melanomas have a relatively low burden of point mutations and a high incidence of copy number variation with multiple amplifications of genes such as *CCND1* (cyclin D1) and *KIT*.[25,136,137] Somatic *TERT* translocations, copy gains, and missense and promoter mutations, or germline events, were recently described in 41% of patients.[138] Mutually exclusive mutations of *BRAF*, *NRAS*, and *KIT* are seen in a subset of cases,[126,139] and also kinase fusions have been identified.[31] Some of these events may represent examples of melanomas of other pathways occurring in acral sites.

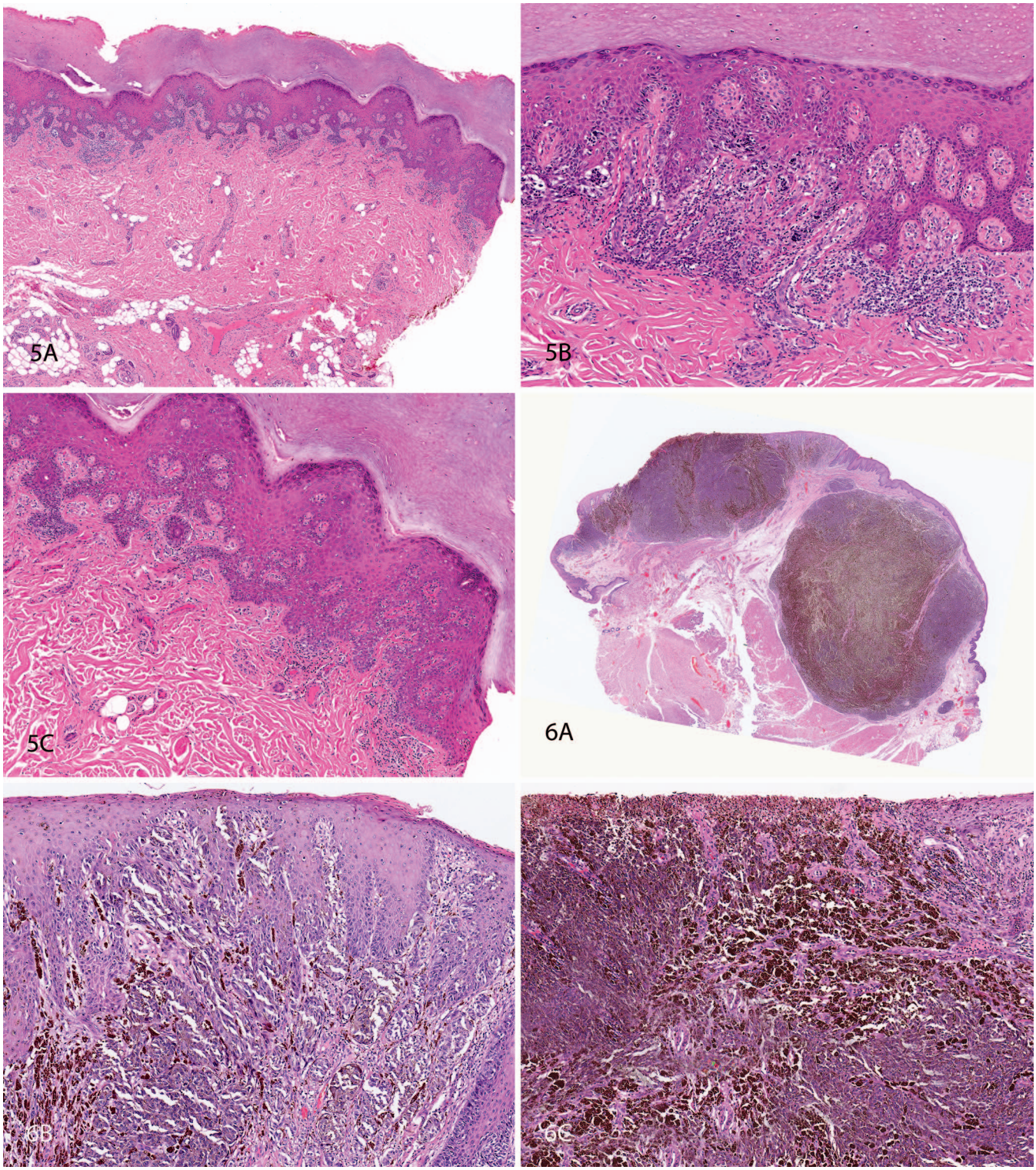

Figure 5. *Acral lentiginous melanoma in situ. No cumulative solar damage. A, In this melanoma reexcision specimen, there is obvious cellular proliferation at the interface especially toward the left of the specimen. B, In this region, there are a few nests and there are single cells along the junction (a lentiginous pattern), associated with a focally prominent infiltrative lymphocytic response. C, At the periphery of the specimen, there is a much less cellular proliferation, which is also amelanotic, constituting subtle involvement of the resection margin, an important consideration in the evaluation of resections of lentiginous melanomas (hematoxylin-eosin, original magnifications ×50 [A], ×200 [B], and ×100 [C]).*

Figure 6. *Mucosal melanoma. No cumulative solar damage. A, In this resection of an anal lesion, there are 2 separate bulky vertical growth phase nodules, associated with a radial growth phase component. B, The radial growth phase component is predominantly lentiginous, with invasion of the lamina propria by cells that differ from those of the vertical growth phase nodules. C, In a vertical growth phase nodule, superficially ulcerated, heavily pigmented spindle cells predominate, with numerous associated melanophages (hematoxylin-eosin, original magnifications ×5 [A], ×100 [B], and ×200 [C]).*

Pathway VI: Mucosal Melanoma

Epidemiology.—Defined as melanoma occurring in a mucous membrane, these lesions occur most commonly in genital sites, in the oral and nasal cavities, and the conjunctiva, and rarely other mucosae.[140] These lesions occur with about equal frequency in all races and therefore form a substantial fraction of the melanomas that occur outside of the high-risk regions populated by whites. Risk factors are largely unknown, as there is no known association with sun exposure[141] or evidence for a pathogenic role of chemical carcinogens or viruses.

Clinical Features.—Mucosal melanomas may evolve through an RGP that presents "ABCDE" features and may be recognized clinically in visible regions such as the vulva, the oral cavity, and the conjunctiva.[142] Lesions occurring in nasal sinuses and occasionally in visceral organs are almost never recognized when entirely in the RGP. Because of the difficulties in visualizing these lesions, they commonly present as a bulky tumor that invades and destroys surrounding tissues, sometimes presenting with bleeding and sometimes with pain or discomfort. In a recent study, vulvar and vaginal melanomas had similar molecular characteristics,[143] even though vulvar lesions usually involve skin, indicating that these are closely related and differ from nongynecologic mucosal melanoma (see Genomic Features).

Histopathology.—The RGP of mucosal melanomas typically presents a lentiginous pattern of growth of single cells tending to become confluent along the interface region of usually squamous mucous membranes,[142] and these lesions have been called *mucosal lentiginous melanomas*.[144] There is typically no evidence of solar elastosis,[140] except in exposed sites like the conjunctiva, where solar damage may be etiologic. However, genetic analyses of conjunctival melanomas have revealed that these are related to melanomas from other pathways (ie, a mixture of high-CSD and low-CSD melanomas).[145] There may be a tendency for nesting and for pagetoid scatter into the epithelium but these tend to be relatively limited compared to SSM and occur when the lesion is more advanced. When VGP eventuates, it forms a tumor comparable to that in other pathways of melanoma (Figure 6, A through C). A desmoplastic pattern of VGP is sometimes seen; this likely differs in many respects including tumor mutation burden from DM in high-CSD skin.

Differential Diagnosis.—The major simulators of superficial mucosal melanomas are mucosal melanosis, mucosal lentigines, and atypical mucosal nevi (the latter also simulate tumorigenic melanomas). Occasionally, a nonmelanocytic tumor near a mucocutaneous junction may contain melanin pigment produced by reactive melanocytes, and in addition, metastatic melanomas to mucosal surfaces need to be distinguished from tumorigenic primary melanomas.

Mucosal lentigo, as in other sites, is defined as a patch of hyperpigmentation of basal keratinocytes, with an increased number of melanocytes.[146] Clinically, such lentigines and other macular hyperpigmentations including melanosis and melanoacanthoma may be referred as *melanotic macules*, a histologically nonspecific term.[146] There is overlap clinically and histologically between mucosal lentigines and mucosal melanosis, in which there is hyperpigmentation but the number of melanocytes is not increased, and with mucosal melanoma in situ, in which there is melanocytic atypia and usually at least focal contiguous proliferation of melanocytes along the junction. By definition, nests of melanocytes are absent in a lentigo, and if they were present the differential diagnosis would be between a (lentiginous) nevus and melanoma. Extensive continuous and contiguous proliferation of atypical cells, as well as the presence of some nests, raises concern for melanoma in situ. The literature on mucosal lentigines is scant. In one study, it was noted that melanoma in situ and mucosal melanosis were indistinguishable clinically in a patient with oral mucosal melanoma.[147] It is important to be aware that mucosal lentigines, with varying degrees of atypia, may be seen in the same sites as mucosal melanomas, including especially oral mucosa and the mucocutaneous surfaces of the genitalia, especially the vulva, often presenting considerable difficulties of differential diagnosis and management.[148]

Genomic Features.—The somatic mutation burden is lower than that for CSD melanomas and there are more numerous structural variations.[149] *KIT*[136,149,150] and *NRAS*[151] mutations have been described in a proportion of tumors, but *BRAF* mutations are uncommon,[149] although oncogenic *BRAF* fusions have recently been identified.[151] In contrast, conjunctival melanomas are probably a mixture of high-CSD melanoma, having evidence of solar elastosis and genomic changes indicative of high UV exposure, and of low-CSD melanomas.[152,153]

Pathway VII: Melanoma Arising in a Congenital Nevus

Epidemiology.—Congenital nevi, defined as melanocytic nevi present at birth, occur in about 1% of newborns.[154] Most of these are small lesions clinically not distinguishable from acquired nevi that develop in later life. The congenital nevi are divided into 3 subsets: giant or garment nevi that cover whole regions of the body and are usually not able to be excised; intermediate congenital nevi susceptible to surgical excision; and small congenital nevi defined as less than 2.5 cm in diameter (still considerably larger than most acquired nevi). Melanomas that occur in giant congenital nevi tend to occur during childhood[155] and apparently with a lesser frequency throughout life. Estimates of the lifetime incidence of melanoma in large congenital nevi range widely from 1% to 30%. In a comprehensive review, prospective studies of academic referral centers showed significantly lower average rates of 2% to 5%, in which the average follow-up period varied from 4.5 to 7.3 years.[156] In a registry study, patients with a giant nevus had a 51.6-fold higher risk of developing a melanoma when compared with the general population rates.[157] Intermediate and smaller nevi have been less well studied because of difficulties of ascertainment, definition, and follow-up, but the risk of melanoma arising within any individual lesion is much lower than for giant nevi.

Clinical Features.—Melanomas may develop in the junctional component or in the dermal component of congenital nevi.[156] Lesions that develop in a junctional component with an RGP may have characteristics similar to those of low-CSD melanomas, while lesions that develop in the dermal component have distinctive characteristics. The developing melanoma may be clinically masked by the background pigmented, and often hairy, nevus. These need to be distinguished from the phenomenon of cellular and proliferative nodules in congenital nevi, which are benign lesions typically arising during the first year of life, usually but not always requiring biopsy.[158]

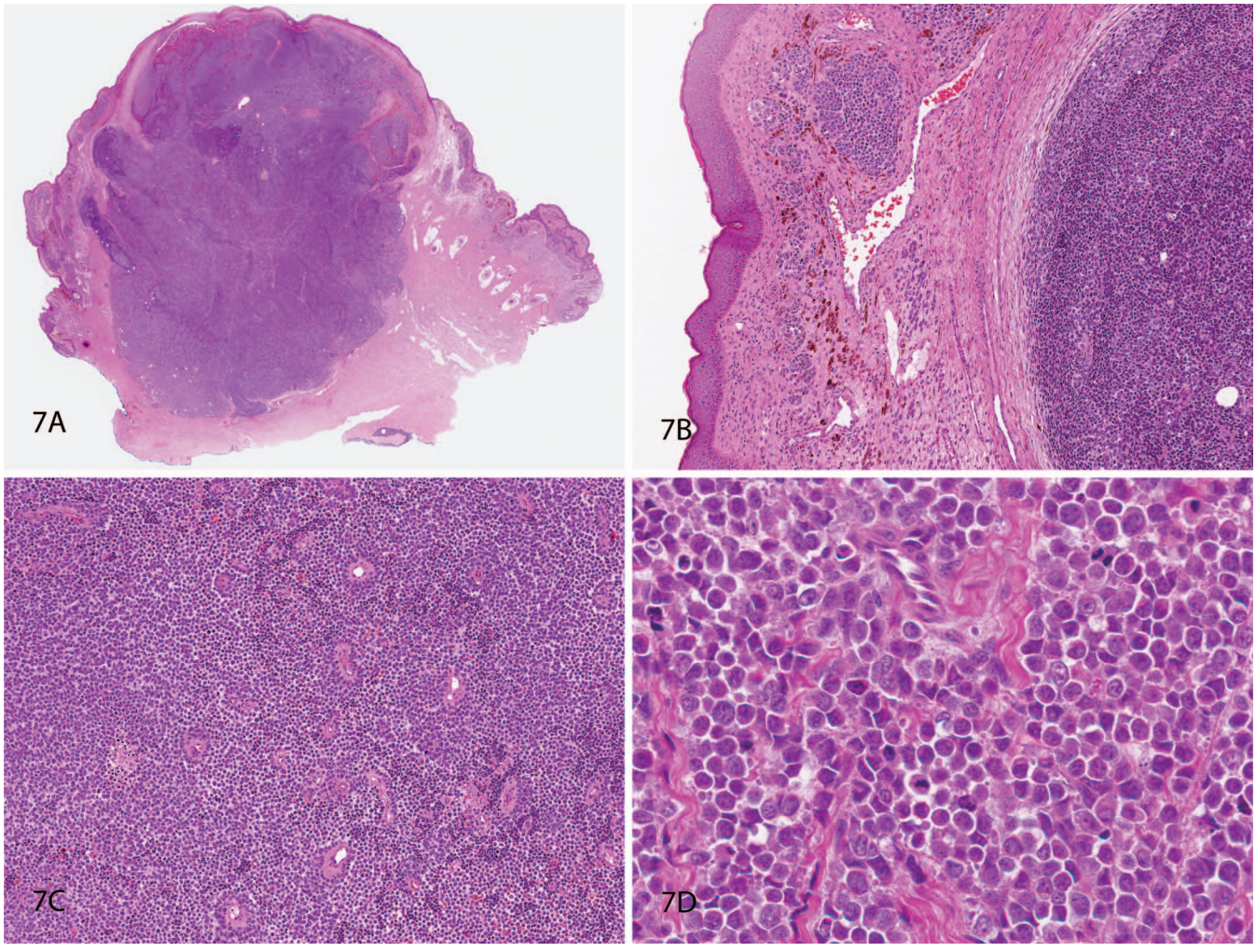

Figure 7. *Melanoma in a congenital melanocytic nevus. No cumulative solar damage. A, There is a bulky nodule that presented as a rapidly growing tumor of the back in a giant congenital nevus in a 4-year-old child. The tumor was not present at birth. B, The nodule contrasts with the background nevus, although there is a subtle tendency to blending between the 2 components. C, The nodule is composed of "small round blue cells," which are quite uniform. D, There is nuclear molding and there are numerous mitoses. Genomic studies could be helpful in considering a diagnosis of proliferative nodule versus melanoma in such an instance. This lesion behaved aggressively, with liver and bone metastases, and ultimately caused the death of the patient within about a year of its presentation (hematoxylin-eosin, original magnifications ×5 [A], ×100 [B], ×200 [C], and ×400 [D]).*

Histopathology.—Melanomas that develop in the junctional component of congenital nevi usually resemble SSM or occasionally LMM histologically.[156] They may progress from in situ to superficially invasive RGP and to VGP nodules. The background congenital nevus is present in contiguity with the melanoma. Melanomas that develop in the dermal component of a nevus present difficulties of accurate diagnosis (Figure 7, A through D). They may present as nodules and tumor masses, which may be composed of epithelioid, spindled, or "small round blue" cells, and may exhibit features of various sarcoma types, such as malignant schwannoma, rhabdomyosarcoma, and liposarcoma.[156,159] Distinction between authentic dermal melanomas and atypical proliferative nodules may be very difficult; however, genomic analysis can be of assistance (see below).

Differential Diagnosis/Simulants and Precursors.—Nodular malignant tumors that occur in congenital nevi need to be distinguished from cellular and proliferative nodules, which occur quite frequently in giant congenital nevi, typically in childhood.[160] These nodules are composed of cells that are usually larger than those in the background nevus. There may be a tendency for blending with the background nevus, or there may be a sharp demarcation. These lesions may have a few or even many mitoses, or there may be no mitoses at all, and such amitotic lesions may be termed *cellular* rather than *proliferative* nodules.[158] Unusual differentiation that may occur in melanoma nodules in congenital nevus does not typically occur in the cellular nodules. Characteristics that can differentiate the lesions from melanoma include lack of high-grade uniform cellular atypia; lack of ulceration and of necrosis within the nodule; rarity of mitoses; evidence of maturation in the form of blending or transitional forms between the cells in the nodule and the adjacent nevus cells; lack of pagetoid spread into the overlying epidermis; and no destructive expansile/infiltrative growth.[158] Genomic studies can be helpful in the distinction (see below).

Genomic Features.—*NRAS* mutations are the most common drivers in large and intermediate congenital

nevi,[161,162] and in the melanomas that arise in them.[163] Lesions known as *congenital pattern nevi*, which are generally less than 1 cm in diameter and have lesional cells extending into the reticular dermis and/or are around or within skin appendages but were not present at birth, usually have *BRAF* mutations and probably represent a subset of acquired nevi.[161,162] In subsets of melanoma, including those arising in giant congenital nevi, TERT expression may be upregulated epigenetically by a methylation-dependent mechanism,[164] while the tumors retain the wild-type genotype.[163] Proliferative nodules, in contrast to melanomas, tend to have whole chromosome number aberrations.[160] In a recent study of 2 lethal melanoma nodules compared to 22 proliferative/cellular nodules, the lethal melanomas both featured expansile nodules of epithelioid melanocytes with high mitotic counts (5–20 mitoses/mm^2), and an ulcerated overlying epidermis. At the genomic level, the proliferative nodules had mostly whole chromosomal copy number aberrations, in some cases accompanied by rare partial chromosomal aberrations, whereas lethal melanomas had highly elevated copy number aberrations involving 6p25 without gains of the long arm of chromosome 6,[160] and/or homozygous loss of 9p21,[165] suggesting that these quite dramatic differences may be reliably predictive of behavior even in atypical cases; however, direct evidence for this is currently lacking.

Pathway VIII: Melanoma Arising in Blue Nevus

Epidemiology.—Blue nevi (BN) are relatively uncommon and risk factors for their occurrence are unknown.

Clinical Features.—Several categories of BN are recognized, most importantly the common lesions variously termed *banal*, *Jadassohn*, *usual*, or *dendritic* BN, and the less common cellular blue nevi (CBN). Other subtypes include epithelioid BN and plaque-type BN,[166] and hypopigmented and sclerosing BN.[167] Typical BN are composed of a relatively sparsely distributed population of pigmented spindle cells with thin dendritic cytoplasmic processes located among sometimes thickened reticular dermis collagen fiber bundles. Cellular blue nevi in addition have areas of confluence of cells that may have clear cytoplasm and form nests. In a characteristic "mixed-biphasic" pattern, fascicles of spindle cells extend between nests of cells with partially clear cytoplasm.[168] Lesions often have a bulbous expansion at the base extending into the subcutis. *Melanoma arising in blue nevus* (MBN) is a term that is preferred to the previously commonly used "malignant blue nevus," because the melanomas occur as a new population of cells usually developing in the background of a CBN, which itself often occurs in a background of a more banal BN. In a recent review of 91 cases, the mean age at diagnosis was 45 years, with a slight male predominance. Metastases were reported in 55% (n = 50), of which 16 had metastases at the time of diagnosis, 16 developed metastases within the first year, and 18 within 5 years of initial diagnosis. The mean Breslow thickness was 6.8 mm at the time of diagnosis (n = 39).[169]

Histopathology.—MBN presents as a tumorigenic proliferation within a background lesion, usually a CBN, and is usually diagnosed relatively late because early changes are perhaps obscured by the presence of the precursor lesions (Figure 8, A through C). Ulceration may occur; however, often the lesions are deep-seated and are recognized only because of an increase in size of a long-standing preexisting lesion. These melanomas are characterized by tumorigenic proliferation of uniformly large cells with marked anaplastic cytologic atypia, frequent mitoses, and usually the presence of necrosis or ulceration.[166] The diagnosis is therefore usually not in doubt; however, there is probably some morphologic overlap of potentially aggressive cases with that of atypical CBN, leaving room for doubt regarding the diagnosis in some cases.[170] Such lesions probably represent intermediate forms of progression from CBN to melanoma. Genomic studies can assist in these distinctions (see Genomic Features below).

Differential Diagnosis/Simulants and Precursors.—The differential diagnosis of MBN includes BN/CBN, and also melanomas that simulate MBN but can be distinguished by lacking the defining features of a background BN and, more recently, by the characteristic genomic abnormalities.[171] Metastatic melanoma can simulate MBN and can be distinguished by the history and clinical workup, and the lack of a background lesion, perhaps supported by genomic studies.[172] A subset of primary melanomas not originally diagnosed as MBN also contains the characteristic genomic changes, and may perhaps appropriately be reclassified.[171]

Genomic Features.—In a study using comparative genomic hybridization of CBN and malignant BN, the number of chromosomal aberrations (3 or fewer versus more per lesion) correlated with cytologic atypia, a high mitotic rate, the presence of necrosis, and with a diagnosis of malignancy and with aggressive behavior.[173] The genetic alterations in melanomas in BN are distinctive and overlap extensively with those of uveal melanoma.[174,175] Driver mutations occur in the G protein signaling pathway, most often in the genes *GNAQ* and *GNA11*, and infrequently in *PLCB4* or *CYSLTR2* (in both BN and associated melanoma). *EIF1AX*, *SF3B1*, and *BAP1* mutations (characteristically seen in uveal melanomas) are also present in a subset of MBN cases, with *BAP1* and *SF3B1* ^{R625} mutations being present only in clearly malignant tumors. In biphasic lesions with a BN and MBN component, the secondary alterations in *BAP1*, *SF3B1*, or *EIF1AX* are confined to the MBN component, indicating that they are responsible for the malignant transformation. Testing for these mutations, particularly BAP1 IHC, can be a useful diagnostic adjunct to confirm malignancy where there is diagnostic doubt.[6,171,176] Copy number aberrations are more common and often complex in melanomas in BN compared with CBN and atypical CBN. Gains and losses of entire chromosomal arms have also been identified including gains of 1q, 4p, 6p, and 8q, and losses of 1p and 4q.[173,177]

Nodular Melanoma

Epidemiology.—Nodular melanomas most likely can occur in any of the pathways discussed above, and therefore their epidemiologic and genomic features are likely to be heterogeneous.

Clinical Features.—Nodular melanomas have a papular or nodular configuration on clinical evaluation.[178] They may be pigmented and the pigment may be homogeneous or heterogeneous; however, they are commonly amelanotic, presenting as a pink papulonodular lesion. Because they are tumorigenic from close to their initiation, NMs present as rapidly growing lesions. Nodular melanomas have a worse prognosis, on the average, than other melanomas, but this difference disappears, perhaps not completely,[179] when multivariable analyses are done.

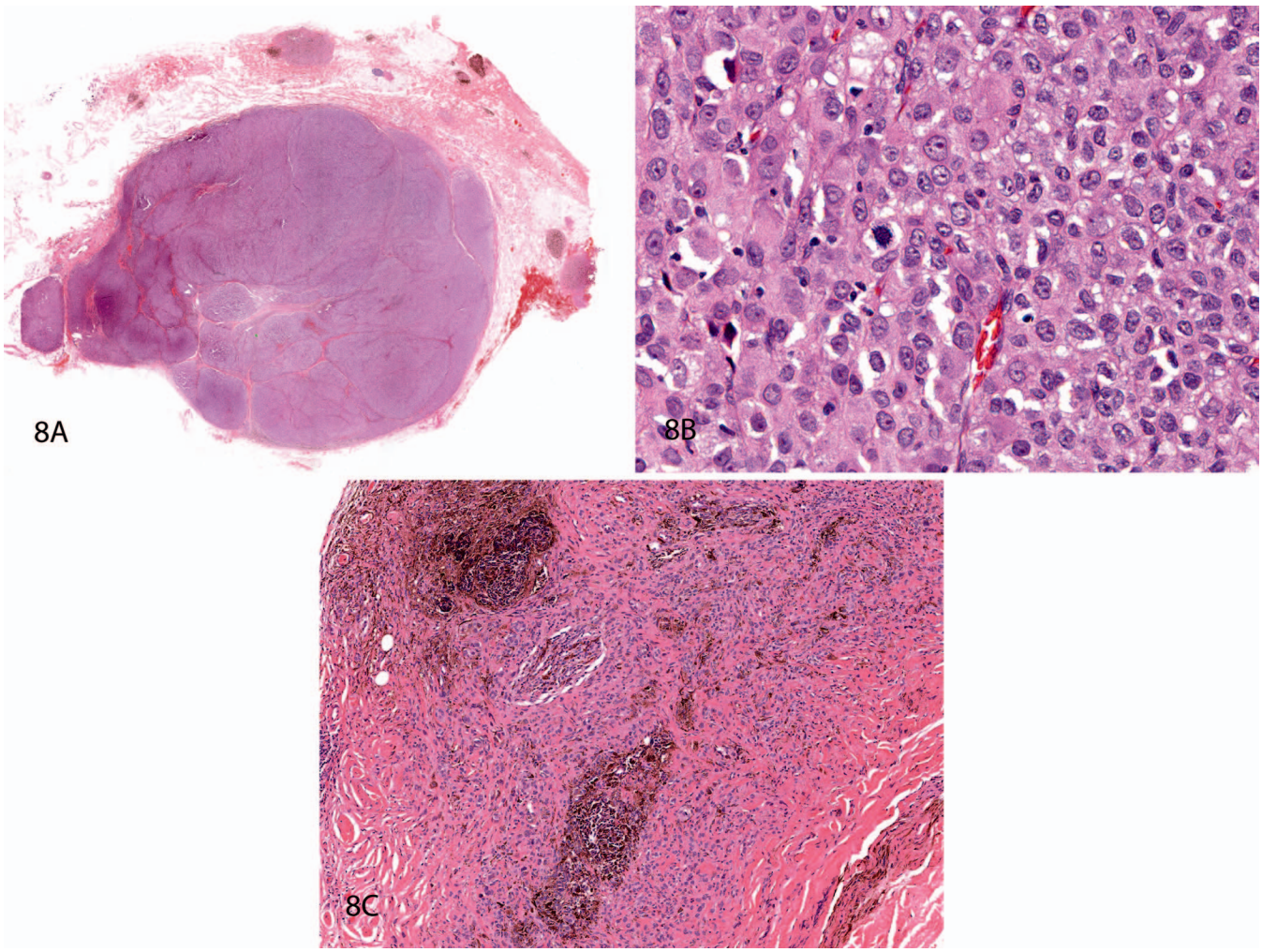

Figure 8. *Melanoma arising in blue nevus. No cumulative solar damage. A, There is a bulky nodule in the subcutis. B, In the nodule, there is a highly cellular proliferation of uniformly atypical melanocytes with frequent mitoses, histologically diagnostic of malignancy. C, In the background, there are "mixed-biphasic" changes of a cellular blue nevus (hematoxylin-eosin, original magnifications ×5 [A], ×200 [B], and ×50 [C]).*

Histopathology.—Despite being relatively small in diameter, NMs can have a significant Breslow depth. However, they share the common feature of being tumorigenic proliferations of uniformly atypical mitotically active neoplastic melanocytes (Figure 9, A through E). The tumors are commonly ulcerated. They are characteristically elevated above the epidermis, indicating accretive growth in an upward direction. A few lesions have a predominantly tumorigenic configuration but may have a few atypical melanocytes in the epidermis. By convention, if these extend beyond 3 rete ridges, they may be considered to represent a preexisting RGP, which can then potentially be classified into one of the other pathways. Otherwise, lesional cells that involve the epidermis in these lesions are quite likely to have been derived from the expanding dermal nodule.

Differential Diagnosis/Simulants and Precursors.—Nodular melanomas must be differentiated from other pink (or variegated) papules, including lesions such as dermatofibromas, nevi, neurothekeomas, neurofibromas, and skin appendage tumors. A difficult problem is posed by superficial metastases of melanoma to the skin as these may be epidermotropic, involving the overlying epidermis and thus closely resembling a primary melanoma. In a recent study, features significantly associated with epidermotropic metastatic melanoma included "a tumor size of less than 2 mm, an absence of tumor-infiltrating lymphocytes and plasma cells, monomorphism, and involvement of adnexal epithelium."[180] The presence of lymphovascular invasion may also be a differentiating feature.[181] Lack of extension of the epidermal component beyond the borders of the dermal component was once emphasized, but there are occasional exceptions to this and other "rules."[182] Features associated with primary NM included "a polypoid (exophytic) configuration, prominent tumor-infiltrating plasma cells (TIPs), a tumor size greater than 10 mm, ulceration, epidermal collarets, a higher mitotic rate, necrosis, multiple phenotypes, significant pleomorphism, and lichenoid inflammation."[180] In multivariate analysis, a logistic regression model including large tumor size, ulceration, prominent TIPs, lichenoid inflammation, and epidermal collarets was highly predictive of primary NM.[180] Rare epidermotropic melanomas may have an "epidermal-only" or "epidermal-predominant" pattern closely simulating in situ or microinvasive melanoma.[180,183] Other epidermotropic metastatic melanomas and superficial dermal metastatic melanomas are well differentiated and may

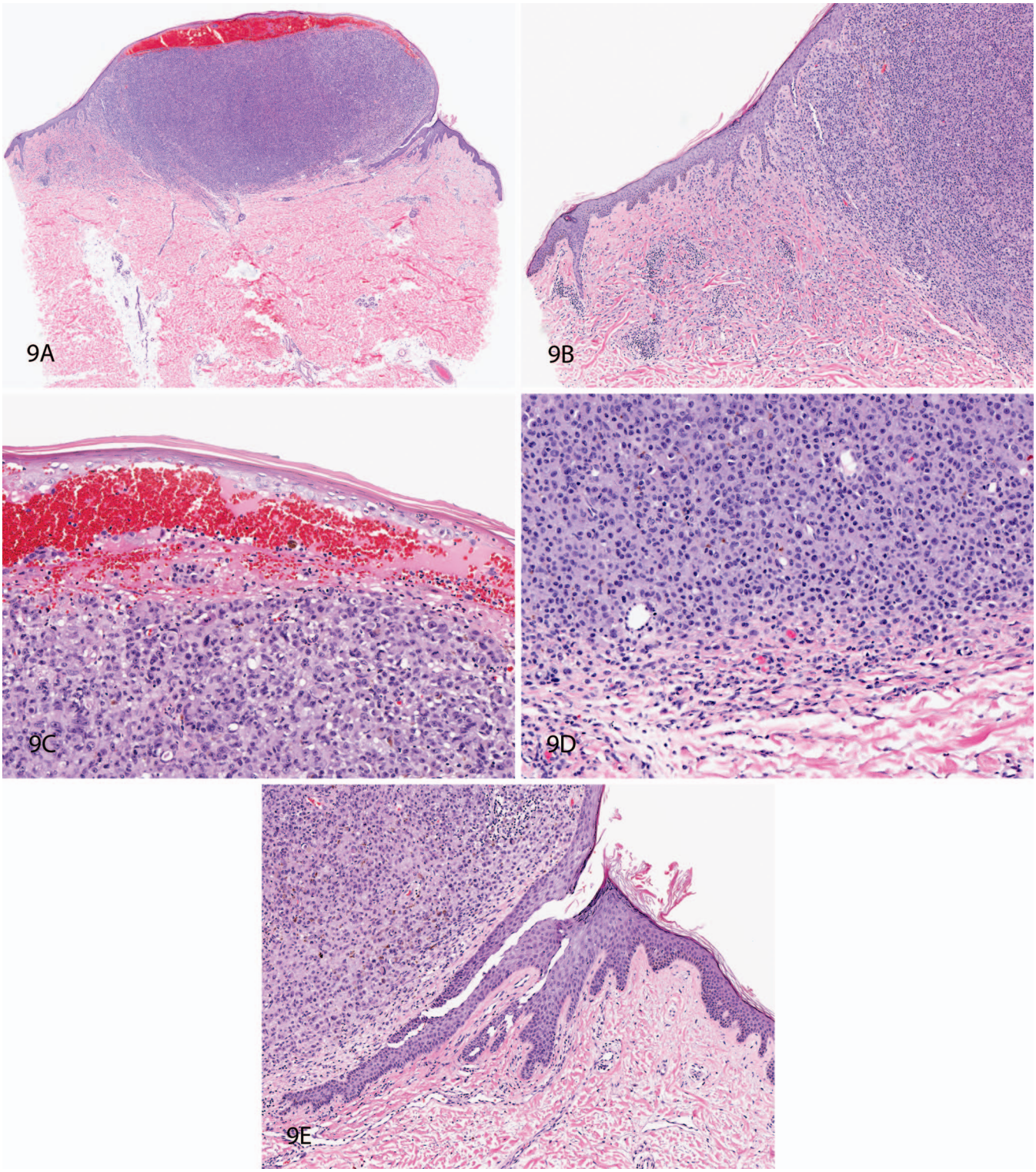

Figure 9. *Nodular melanoma (from Cochran et al,[185] with permission. International Agency for Research on Cancer. World Health Organization. Elder DE, Massi D, Scolyer RA, Willemze R, eds.* WHO Classification of Skin Tumours. *4th ed. Lyon, France: IARC; 2018). A, There is a nodular tumor elevating the epidermis with a collaret on the right-hand side and with a remnant of a nevus on the left. B, The precursor nevus cells contrast with those of the nodule. C, The lesional cells are large, with uniformly atypical nuclei and frequent mitoses. D, There is only slight evidence of maturation to a smaller cell type at the base. E, On the right-hand side there is a collaret and there is no associated in situ or invasive radial growth phase component (hematoxylin-eosin, original magnifications ×5 [A], ×50 [B and E], and ×200 [C and D]).*

simulate nevi (nevoid or differentiated epidermotropic metastatic melanoma or epidermotropic metastatic melanomas with maturation).[184] Genomic studies could be helpful in this distinction.

Genomic Features.—Studies of hotspot mutations in *BRAF* and *NRAS*, and genome-wide copy number analyses have indicated that NMs share the genetic alterations of other melanomas arising in similar settings (CSD or anatomic site).[25,38]

CONCLUSIONS

We have provided a summary of a classification of melanoma that builds on previous work and distinguishes 9 distinct types of melanoma development based on their epidemiology, clinical and histologic morphology, and genomic characteristics (including uveal melanoma, which is not discussed in detail here). Wherever appropriate based on currently known data, each melanoma subtype is placed in a position at the end of an evolutionary lineage (or "pathway") that is founded in its respective precursor lesion. Each precursor subtype has a variable, usually low, risk of progression through stages of evolution culminating in an invasive and tumorigenic melanoma, which in turn has a variable risk of metastasizing and causing death based on continuing evolution.

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