Primary Cutaneous Melanocytic Neoplasms

16

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Contents

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Abstract

This chapter on primary cutaneous melanocytic neoplasms of the skin will discuss three major categories of benign melanocytic neoplasms: common acquired, congenital, and blue nevi. The predominant initiating genomic event in common acquired nevi is a mutation in BRAF, while a significantly smaller percentage have a mutation in NRAS. Mutations in NRAS occur far more frequently in congenital nevi; the ratio of NRAS to BRAF mutations in congenital nevi varies depending on the size of the congenital nevus. Giant congenital nevi are almost exclusively NRAS mutated. Blue nevi commonly have mutations in GNAQ and GNA11 and likely have a distinct melanocytic precursor cell compared to many, but not all, common acquired nevi. This chapter will highlight how specific mutations and melanocytic precursor cell types impact morphology of benign melanocytic nevi and how these factors can be integrated into a more reproducible classification system. The author also discusses two major subtypes of melanoma: those occurring on non-chronically sun-damaged skin, which have frequent BRAF mutations, and melanomas occurring in chronically sun-damaged skin, which have less frequent BRAF and NRAS mutations but have occasional mutations in c-Kit or NF1. Likewise, the author discusses how the mutation and cell of origin in these melanomas relate to morphology and ultimately can be used for a more robust classification system.

Keywords

Nevi · Common acquired · Congenital · Blue nevi · Melanoma · Genomics

Introduction

While melanocytic neoplasms can arise in a variety of organs, including in the epithelium of the gastrointestinal system and other mucosal sites, the eye, and the central nervous system, the skin is the site of origin to the majority of benign and malignant melanocytic neoplasms. It has long been recognized that melanocytes originating from neural crest cells migrating along specific routes colonize the epidermis of the skin. More recently some data suggests that a second population of melanocytes are normal inhabitants of the dermis (Fernandes et al. 2004). These cells are derived from Schwann cell precursors migrating along peripheral nerves into the dermis and reside in the dermis in the adventitia of nerve fibers and other adnexa.

Factors distinguishing distinct subtypes of melanocytic neoplasms of the skin and ultimately affecting the clinical and histologic presentation include derivation from epithelial-associated melanocytes versus nonepithelial-associated melanocytes and specific genetic alterations. Most data correlating genetic features to morphology suggest that primary activating mutations are most strongly correlated to morphologic and clinical features. Some exceptions to this rule exist, primarily in various patterns of combined nevi where a second clonal population defined by a subsequent genetic alteration is seen. Initiating mutations in melanocytic neoplasms are typically activating point mutations in the mitogen-activated protein (MAP) kinase pathway or translocations in receptor tyrosine kinases (RTKs), which typically occur in a mutually exclusive pattern. This chapter will primarily discuss common acquired, congenital, and blue nevi and the

most common forms of melanoma, including melanocytic cell type of origin and initiating driver mutations and how these relates to morphologic and clinical features.

Common Acquired and Dysplastic Nevi

Definition

By definition, a nevus is a benign clonal proliferation of melanocytes arranged in nests. A nest is defined by three or more aggregated melanocytes. In contrast to melanoma, nevi are organized, limited proliferations of melanocytes typically arranged in a predominance of nests over single cells and have some level of symmetry and reasonably well-defined borders (Fig. 1).

Clinical and Histologic Features

The development of nevi is a function of environmental and genetic factors. The only known modifiable environmental variable is ultraviolet (UV) radiation exposure. Multiple genetic factors are involved: (1) skin type along with MCR1 receptor type and other pigmentary related genes, which all influence an individual's response to UV and ability to protect themselves from UV radiation through melanin production; (2) germline mutations in tumor suppressor genes, which may influence whether senescence of newly proliferating melanocytic neoplasms is immediate or delayed; and (3) immune-related genes, which can also influence immune-mediated clearance of newly initiated melanocytic neoplasia. Two different twin studies demonstrate

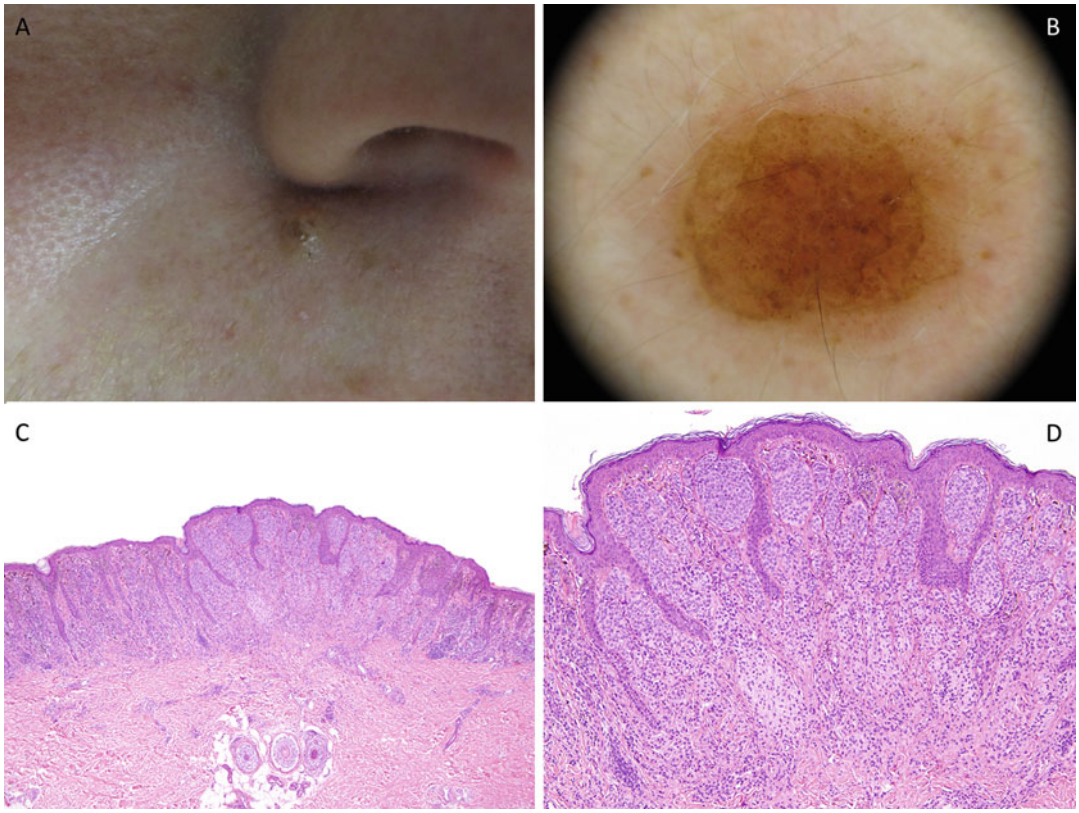

Fig. 1 This is an example of a common acquired nevus from the face of a 30-year-old woman. (**a**) Clinically, it is a 4 mm brown well-circumscribed exophytic papule. (**b**) Dermoscopically, one sees a rather uniform globular pattern. (**c** and **d**) Histologically, there is a predominantly nested pattern of melanocytes involving both the epidermis and dermis. The dermal component shows good maturation and the cells lack significant atypia.

a significant heritability component to total nevus counts. In both studies, monozygotic twins had significantly greater similarity in total nevus counts in comparison to dizygotic twins (Wachsmuth et al. 2001; Lee et al. 2016). Both studies also concluded that genetics play a greater role in nevus counts than sun exposure history. However, there is also convincing epidemiologic data documenting a relationship between history of ultraviolet radiation exposure and nevus counts (Dulon et al. 2002; Wiecker et al. 2003; Aalborg et al. 2009). These studies demonstrate a relationship between total nevus counts and sun exposure history and the distribution of nevi and sun exposure history. Hence, the development of acquired nevi is a combined function of multiple genetic factors and ultraviolet exposure (Table 1).

Acquired nevi may be completely flat (macular) or raised (papular). Most common acquired nevi are less than 6 mm in size and are relatively symmetric and uniform in color. By dermoscopic assessment, most have either a reticular pattern or globular pattern. The reticular pattern is the result of melanocytes and their melanin pigmentation aggregating along rete ridges, while a globular pattern is the result of distinct pigmented nests of melanocytes. Histologically, nevi can have nests strictly associated with the epidermis (junctional), in both the epidermis and dermis (compound), or strictly in the dermis (dermal). In children, most nevi are compound or dermal, while junctional nevi are uncommon. In adults, all three types of nevi can be seen. Most acquired nevi occur during the first two decades of life, but new nevi may occur at any age. In a study of 182 adult patients followed in an outpatient dermatology setting, 50 (27%) developed at least 1 new nevus (Oliveria et al. 2013). Most of the newly occurring nevi were reticular or reticular-globular, which are patterns suggestive of junctional or compound nevi, respectively.

Two typical histomorphologic patterns of common acquired nevi have been designated as Miescher's or Unna's nevus. Unna's nevi are compound or dermal exophytic nevi with a mammillated surface with nests of melanocytes in the papillary dermis. Miescher's nevi are smooth, dome-shaped papules, which are typically entirely dermal. Miescher's and Unna's nevi typically lack significant nuclear atypia or mitotic activity, although mitoses may rarely be seen, often in females of gestational age. Microscopically the lesions are predominantly organized in nests, and the dermal component is characterized by good maturation with decreasing nest and cell size with descent into the dermis. Cells in the deep dermis typically have inconspicuous nucleoli and pigmentation. If there is significant melanin pigmentation, it is typically superficial and lost with descent.

The term dysplastic nevus is controversial. It was originally utilized to clinically describe the large and irregular nevi seen in cohorts of patients with familial melanoma. The term has evolved considerably over time. While the subset of nevi the term originally referred to was probably a lot more limited the way it is currently used in practice most Caucasian individuals would have at least one dysplastic nevus. The WHO has created histomorphologic criteria for the designation. This requires both major criteria and two of four minor criteria to be met.

Major criteria

1. Basilar proliferation of atypical melanocytes that extends at least 3 rete ridges beyond the dermal component.
2. Organization of this proliferation in a lentiginous or epithelioid cell pattern.

Minor criteria

1. Lamellar fibrosis or concentric eosinophilic fibrosis.
2. Neovascularization.
3. Host response.
4. Fusion of rete ridges.

As indicated in the major criteria listed above, in contrast to Unna's or Miescher's nevi, these lesions have a broader intraepidermal component that extends at least 3 rete ridges beyond the dermal component (Fig. 2). The presence of this broad intraepidermal component is significant as multiple studies have shown that having larger acquired nevi is linked to an elevated risk for melanoma. Dysplastic nevi often also have greater nuclear atypia and architectural disorder than Unna's or Miescher's nevi. This may include areas with considerable single cell lentiginous

Table 1 Characteristics of distinct subsets of melanocytic neoplasms

Entity	Cell of origin	Clinical presentation	Histologic features	Common initiating genomic event
• **Common acquired nevi**	• Mostly epidermal-derived melanocyte Some acquired nevi with a congenital histologic pattern may be from dermal-derived melanocyte	• Variable presentation that may include both macular and papular lesions typically less than 6 mm in size that are relatively symmetric and uniform in color. • Miescher's nevi are commonly smooth dome-shaped lesions, Unna's nevi have a exophytic mammillated surface	• May be junctional, compound, or dermal • Miescher's and Unna nevi do not have shouldering, have nests with melanocytes without significant atypia and normal maturation seen extending from epidermis to deeper dermis. Acquired nevi in later life may take the form of lentiginous junctional or lentiginous compound nevus. These are typically small <6 mm with predominance of melanocytes typically aggregated around the rete ridges and small nests of melanocytes are seen in the dermis	• BRAF (85%) • NRAS (5%)
• **Dysplastic nevi**	• Likely epidermal-derived melanocyte	• Usually have a macular component. May be >6 mm in size and may also have some slight color variation and border irregularity	• Junctional component extends at least 3 rete ridges beyond dermal component (shouldering). Have a nested or lentiginous proliferation of melanocytes in epidermis. Bridging, periretal fibroblasia, host response, and perivascularization are all common	
• **Congenital nevi**	• Dermal-derived melanocyte	• Nevi present at birth of within the first few months of life with variable color ranging from tan to black and often with irregular borders • Small – <1.5 cm • Medium – 1.5–20 cm • Large – 20–40 cm • Giant – >40 cm	• In contrast to common acquired nevi, congenital nevi tend to extend deeper into the dermis and subcutaneous tissue. Melanocytes tend to track along the neurovascular or adnexal structures and dissect the collagen bundles	• NRAS (80% large) • BRAF (60% small-medium)
• **Blue nevus** • **Conventional** • **Cellular blue** • **Plaque-type** • **Nevus of ito** • **Nevus of ota**	• Dermal-derived melanocyte	• Conventional – Dorsal surfaces of the extremities • Cellular type – Along the cranio-sacral axis • Plaque type – Segmental distribution • Nevus of ota – Involves the 1st and 2nd division of trigeminal nerve and can involve the cheek,	• Blue nevus – Dendritic shaped melanocytes with melanophages often in a sclerotic stroma • Cellular blue – In addition to dendritic melanocytes have nests and fascicles of oval to spindle shaped melanocytes often with intervening dendritic melanocytes and melanophages as seen in conventional blue nevi. The cellular fascicles often form	• GNAQ (65%) • GNA11 (10%)

(*continued*)

Table 1 (continued)

Entity	Cell of origin	Clinical presentation	Histologic features	Common initiating genomic event
		temple, conjunctiva, and retina • Nevus of Ito – Find the nerve associated with this, occurs on the shoulder, supraclavicular, or scapular region along areas of supraclavicular and lateral brachial cutaneous nerves	a buttress against the subcutaneous tissue	
• **Malignant blue nevi**	• Dermal-derived melanocyte	• Typically occur in the same distribution as cellular blue nevi along the cranio-sacral axis	• Nests of oval shaped melanocytes that become highly expansile • Morphologic clues to malignancy include frank epithelioid transformation, zones of necrosis, high grade nuclear atypia, and elevated mitotic activity	
• **Melanoma of non-CSD skin/** • **Intermittently sun-damaged skin**	• SSM – Epidermal based melanocytes • Nodular – Either epidermal or dermal-derived melanocytes	• SSM most likely to follow the ABCD rule • Nodular may present as amelanotic or pigmented nodule	• Lack of aggregates of amorphous solar elastotic bundles; more likely to have a nevus component • SSM have radial growth phase that extends at least 3 rete beyond dermal component • Nodular component directly enter vertical phase with no preceding radial growth but often do not meet full criteria for MIS in epidermis but may have small intraepidermal aggregates of atypical cells with lentiginous or pagetoid growth pattern	• BRAF (50%) • NRAS (30%)
• **Melanoma of CSD skin**	• Lentigo maligna and SSM – epidermal-derived melanocyte • Nodular – either dermal or epidermal • Desmoplastic or dermal spindle cell – likely epidermal-derived dermal, although not known with certainty	• Predominantly occur in the head and neck region or other areas with excessive UV exposure; typically diagnosed between 60–80 years • Lentigo maligna type appears as a variably pigmented patch on a background of poikilodermatous skin	• LMM often grows as single atypical melanocytes in a broad lentiginous growth pattern along the DEJ with extensive adnexal involvement. Nesting is often a later stage phenomenon	• KIT (20%, LMM pattern) • NF1 (25% desmoplastic melanoma; CSD) • BRAF (15%)

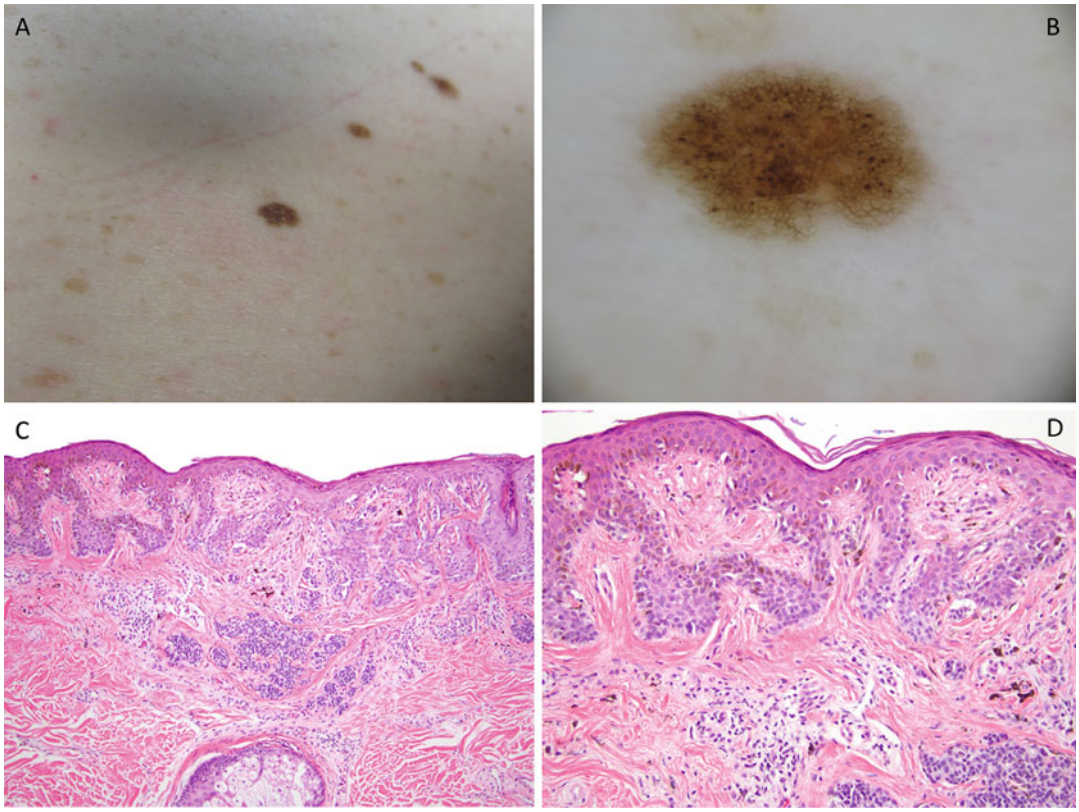

Fig. 2 (**a**) A clinically dysplastic nevus that measures to greater than 6 mm in size and has an irregular border grossly. (**b**) Dermoscopic assessment shows reticulated background with variably sized darker granules distributed throughout the whole lesion. There is slight loss of network towards the center of the lesion. (**c**) Low power magnification shows a dysplastic nevus with nests of melanocytes at the DEJ and within the dermis. There is shouldering, bridging, and periretal fibroplasia. (**d**) Higher power magnification showing typical architecture of a dysplastic nevus with bridging and periretal fibroplasia

growth along the dermal-epidermal junction, focal upward scatter or intraepidermal melanocytes (pagetoid spread), some asymmetry, less sharply defined lateral circumscription, and focal cell aggregates with considerable nuclear atypia. However, the association of other morphologic features of dysplastic nevi to an individual's risk for melanoma is more controversial (Elder 2016).

There can be morphologic overlap between the more atypical examples of dysplastic nevi and the radial growth phase of melanoma. The primary controversy over dysplastic nevi is in regards to whether they have a higher risk than other nevi to transform to melanoma or are intermediaries between common acquired nevi and melanoma. Strong evidence shows that individuals and families who possess clinically atypical nevi in higher numbers and of greater size are at significantly higher risk for melanoma overall (Goldgar et al. 1991; Tucker et al. 1997). Although in a study reviewing histologic dysplasia and diameter of melanocytic neoplasms, diameter of the lesion was the only variable which was statistically correlated with an individual's risk for melanoma (Shors et al. 2006). Genetic studies have found multiple pathogenic mutations in morphologically intermediate (i.e., dysplastic) nevi yet only a BRAF V600E mutation in unequivocally benign nevus cells (Shain et al. 2015). Hence, while theoretically one might expect dysplastic nevi to

have a higher risk for transformation, most epidemiologic data suggest they are for the most part relatively stable lesions with a very low risk for transformation to melanoma (Marks et al. 1990; Tucker et al. 2002; Tsao et al. 2003).

Initiating Oncogenic Events

The initiating driver mutation in common acquired nevi is approximately 85% BRAF and 5% NRAS (Pollock et al. 2003). While BRAF and NRAS mutant nevi may be seen in both sun exposed and sun protected areas, the epidemiologic correlation of nevus counts and distribution with sun exposure suggest there is a relationship between BRAF mutations and UV exposure (Thomas et al. 2007). However, the V600E mutation, which is by far the most common mutation seen in BRAF mutated common acquired nevi, is not a UV signature mutation (Landi et al. 2006; Nguyen et al. 2010).

Cell of Origin

Historically, it was proposed that all common acquired nevi have a life cycle beginning in the epidermis, melanocytes drop into the dermis to become compound, and later become dermal after fading of the junctional component (Unna 1893). This life cycle certainly occurs in some nevi and has been documented in studies and observed by most dermatologists following nevus patients with total body photography over time. However, the observation that dermal and compound nevi far outnumber junctional nevi in children while junctional nevi occur much more frequently in adults suggests that many nevi occurring in younger childhood may have a separate pattern of development. It may be that the melanocytic cell type of origin has an impact on this pattern of development. Specifically, if the cell of origin is an epithelial-derived melanocyte, this may result in a junctional or compound nevus, which may go through the above described life cycle. Common acquired nevi that have histomorphologic features of congenital nevi, such as tracing adnexa and deep extension between collagen, may originate from dermal-based melanocytes. This theory would be consistent with the finding that junctional nevi probably have the highest correlation to sun-exposed sites, whereas nevi that occur in sun-protected sites are often compound or dermal. However, this is not known with certainty.

Senescence and Other Factors Impacting Phenotype

Further mutagenic events may also impact the phenotypic features of common acquired nevi. In a study demonstrating the genetic evolution of benign nevi to melanoma, it was shown that morphologically intermediate lesions had more mutagenic events than obviously benign precursor lesions (Shain et al. 2015). This has also been demonstrated in the past with clonal nevi in which a secondary subclone with greater atypia emerges from an otherwise ordinary nevus (Ball and Golitz 1994). In contrast to initiating oncogenic events that are typically activating mutations, subsequent genomic events are frequently loss of function alterations in tumor suppressor genes.

Other factors that can impact the morphologic features of a nevus include many innate host factors such as the host's genetic, epigenetic (methylation changes), and immune control of senescence — basically how quickly the cell-intrinsic or extrinsic mechanisms can arrest the proliferation of the melanocytic cells. This may be particularly impactful on the size of the nevus. The mechanisms of senescence include: oncogene induced senescence, in which oncogenic activation of the MAP kinase pathway triggers growth arrest through the tumor suppressors p16 or p21; immunosurveillance-mediated senescence, in which the immune system removes neoplastic melanocytes; or replicative senescence, in which telomere shortening induces growth arrest. Telomerase lengthens the telomeres. It has recently become apparent that clonal TERT promoter mutations occur at quite an early stage in the genetic evolution of nevi to melanoma

(Shain et al. 2015). A selective growth advantage of nevus cells for TERT promoter mutations suggests that, even at the nevus level, the cells are turning over and replenishing themselves. Hence, arrest of nevus cells in a benign stage is continually dependent on the above-discussed mechanisms of growth arrest.

Risk for Melanoma

All melanocytic nevi can potentially be transformed to melanoma, and it has been demonstrated that the predominant manner in which this occurs is acquisition of additional genomic alterations as a result of UV mutagenesis. It is unclear if morphological clues can predict which lesions are at greatest risk for transformation. Many studies evaluating melanoma arising in nevi suggest that there is no greater risk of transformation of a dysplastic nevus than other common acquired nevi (Tsao et al. 2003). In fact, the most common subtype of nevus found in association with a melanoma is the conventional common acquired nevus (Marks et al. 1990). Although there may be some bias in that it may be more difficult to clearly delineate a dysplastic nevus from melanoma, compared to delineating other common acquired nevi from melanoma. In addition to primary activating oncogenic mutations at the molecular level, dysplastic nevi often also have loss of function mutations with loss of heterozygosity involving CDKN2A or TP53 (Hussein and Wood 2002). The ACS reports approximately 80,000 new melanomas per year and 30%, or 24,000, are estimated to arise from a precursor nevus (Siegel et al. 2016). When one considers the astronomical number of nevi that qualify for the current definition of "dysplastic," one can see that the per annum rate of transformation of any given dysplastic nevus to melanoma is quite small, which supports the idea that these lesions are stable neoplasms.

From an epidemiologic perspective, considering that among acquired benign melanocytic nevi 85% are BRAF mutated and 5% are NRAS mutated, while in malignant melanocytic neoplasms, 50% are BRAF mutated and nearly 30% are NRAS mutated, there is reason to suspect that NRAS mutated neoplasms have a higher risk of progression. From a molecular perspective, this would also be logical, since NRAS can simultaneously activate both the MAP kinase pathway and the PI3 kinase pathway, while BRAF is further downstream and only activates the MAP kinase pathway (Table 2).

Congenital Nevi

Definition

Congenital melanocytic nevi (CMN) are present at birth and occur in utero or within the first year of life and present in approximately 1% of infants. CMNs have been classified based on size as small (<1.5 cm in diameter in the adult), medium (1.5–20 cm), large (>20 cm), and sometimes giant (>40 cm) (Alikhan et al. 2012). In contrast to the common occurrence of small CMNs, larger CMNs have an estimated incidence of 1 in 20,000 individuals (Castilla et al. 1981). The term "tardive CMN" refers to nevi not present at birth but that become apparent within the first 2 years of life.

Clinical and Histologic Presentation

Most small and medium-sized congenital melanocytic nevi are fairly uniform in color with well circumscribed borders. They are often raised and sometimes can have a papillomatous appearance. Mature terminal hairs may be present. These lesions can occur on any area of the body. Special consideration needs to be given to giant congenital nevi particularly those in a craniosacral distribution. The melanocytic proliferation in these cases can extend into the meninges and may even involve the brain and spinal cord. This is referred to as leptomeningeal melanocytosis or neurocutaneous melanosis. Potential complications from this include hydrocephalus or primary leptomeningeal melanoma. The risk of neurocutaneous melanosis is particularly high for giant congenital nevi along the craniosacral axis with

Table 2 Distinct genomic pathways to melanoma

Gene	Type of alteration	Entities	Common secondary event involved in malignant transformation	Type of alteration
BRAF	Point mutation	Common acquired nevi Dysplastic nevi Congenital nevi Melanoma of non-CSD skin	CDKN2A	Deletion, mutation
			TERT	Mutation, amplification
			PTEN	Deletion, mutation
			ARID1A, 1B and 2	Deletion, mutation
			SMARCA4	Deletion, mutation
NRAS	Point mutation	Common acquired nevi Dysplastic nevi Congenital nevi Melanoma of non-CSD skin	CDKN2A	Deletion, mutation
			TERT	Mutation, amplification
			PTEN	Deletion, mutation
			ARID1A, 1B and 2	Deletion, mutation
			SMARCA4	Deletion, mutation
GNAQ/ GNA11	Point mutation	Blue nevi (cellular, plaque-type, nevus of ota, nevus of ito, Mongolian spots) Uveal melanoma	6p25	Gains
			SF3B1 (2q33)	Mutation
			BAP1	Deletion
			C-MYC	Amplification
KIT	Point mutation	Melanoma of CSD skin Acral melanoma[a] Vulvar melanoma[a] (Yelamos et al. 2016)	N/A	
NF1	Point mutation	Melanoma of CSD skin (desmoplastic and other CSD)	N/A	

[a]Not discussed in this chapter
N/A Not applicable

many satellite lesions (DeDavid et al. 1996; Marghoob et al. 2004; Kinsler et al. 2008).

By dermoscopy, small and medium-sized congenital nevi often show a regular reticular network, a globular pattern with a cobblestone appearance or just diffuse homogeneous pigmentation. Giant congenital nevi may have greater heterogeneity with distinct areas showing either a reticular, globular, or homogeneous pattern. Other common dermoscopic findings in congenital nevi include perifollicular hypo or hyperpigmentation and milia-like cysts. The characteristic histologic changes in congenital nevi include tracing of adnexal structures in the dermis with nests and aggregates of melanocytes in the hair follicle, eccrine glands, and neurovascular bundle. Single melanocytes can also be seen tracking deeply into the dermis and splaying between the collagen fibers (Fig. 3). Some nevi occurring later in life, including in adulthood, can have these histologic features but by history are not congenital in nature. These have been termed "nevi with a congenital pattern." It is likely that these are common acquired nevi that originate from a nonepithelial derived melanocyte, which results in the characteristic growth pattern of tracing adnexa.

Congenital nevi can develop benign nodular proliferations of melanocytes which can mimic melanoma known as proliferative nodules (Fig. 4). Proliferative nodules can develop in any

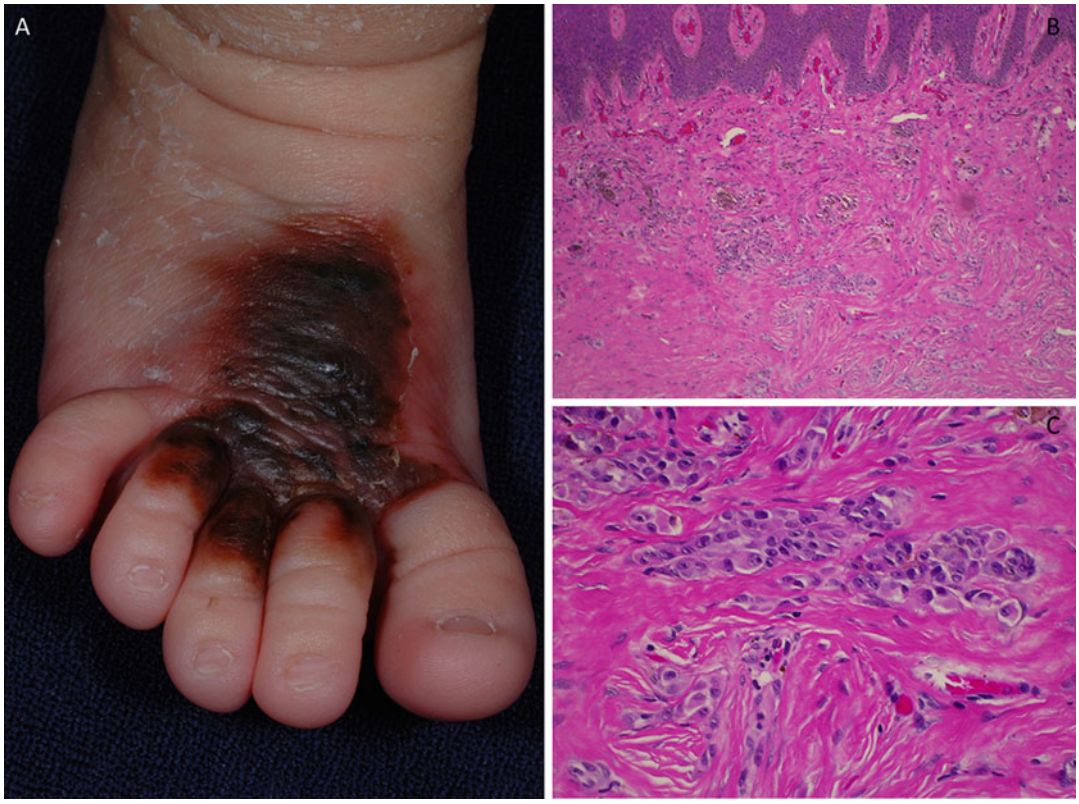

Fig. 3 (**a**) This is an example of a medium-sized (1.5–20 cm) congenital nevus on the dorsal foot of a newborn. (**b**) Low power histology shows small nests and single melanocytes along the DEJ with a predominance of nests in the dermis. (**c**) The dermal nests are seen dissecting through thick bundles of collagen extending through the reticular dermis.

sized congenital nevus and at any age, but are most characteristic of giant congenital nevi in early childhood or infancy (Phadke et al. 2011). Distinct morphologic patterns for proliferative nodules have been identified including nodular proliferations of epithelioid melanocytes, small round blue cell-like proliferations, neurocristic proliferations, spindle cell sarcomatous proliferations, the entire spectrum of blue nevus-like proliferations, and nevoid melanoma-like proliferations. Cytologic atypia and considerable mitotic activity greater than 15/mm^2 can be seen, particularly in small round blue cell or spindle cell sarcomatous patterns. Distinction from melanoma can be challenging. Features favoring melanoma include sharp demarcation from the congenital nevus component, high grade nuclear atypia throughout, high levels of mitotic activity greater than 5/mm^2 in a proliferation of epithelioid cells with high grade atypia, and zones of necrosis. Cytogenetically, proliferative nodules often have whole chromosomal copy number changes, while melanomas typically have clonal segmental chromosomal aberrations (Bastian et al. 2002; Yelamos et al. 2015a). The incidence of proliferative nodules in giant congenital nevi is estimated to be between 3 and 19%. In the author's experience, they are far more common than melanoma arising in a giant congenital nevus.

Initiating Oncogenic Event

Similar to common acquired nevi, the most common initiating oncogenic events in congenital nevi are BRAF or NRAS mutations. The frequency of these mutations varies depending on

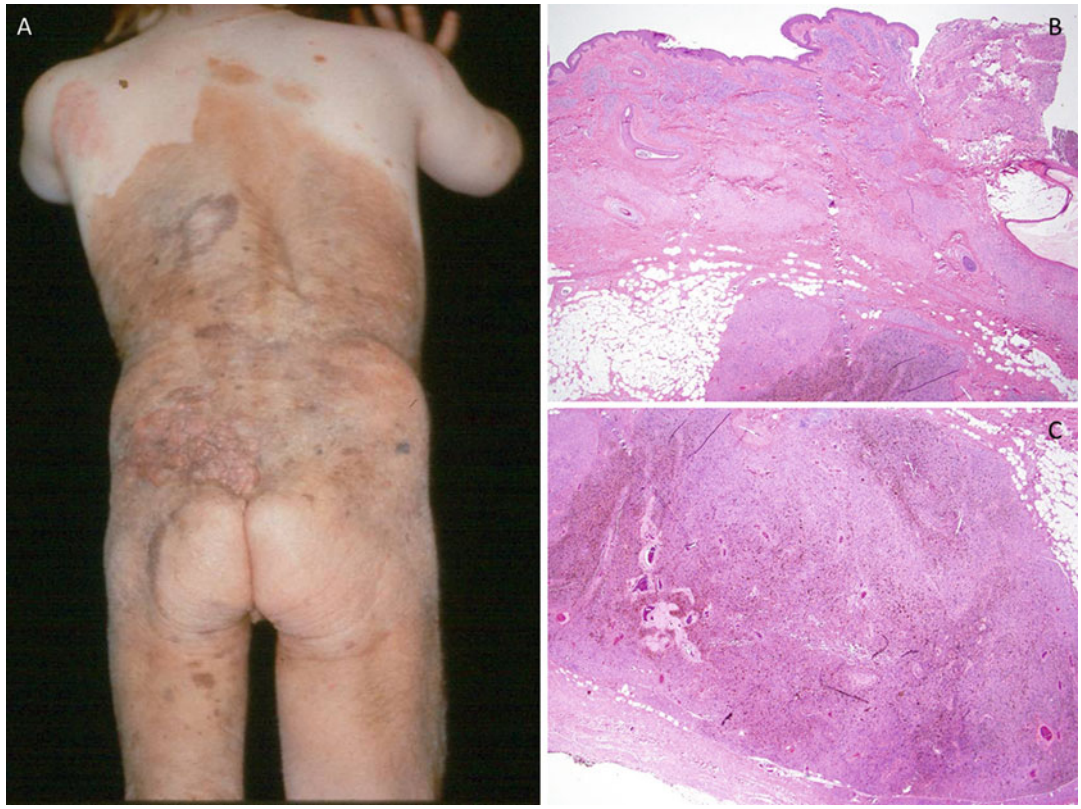

Fig. 4 (**a**) Giant congenital nevus in a truncal distribution with numerous papular and nodular proliferations of various sizes seen on the left lower back. This pattern of giant congenital nevus involving the cranio-sacral axis has a high risk for neural involvement. (**b**) The low power histology shows predominantly dermal involvement of the congenital nevus with melanocytes nesting around adnexal structures and dissecting collagen bundles. At the base, a proliferative nodule can be seen. (**c**) Higher power magnification reveals a benign proliferative nodule with a cellular blue nevus-like patter occurring in a giant congenital nevus

the size of the congenital nevus. In one study of 62 congenital nevi defined by presence at birth, the vast majority of large congenital nevi resulted from mutations in NRAS. In medium-sized congenital nevi, the ratio of NRAS:BRAF mutations was 5:3 and in small congenital nevi the ratio of NRAS:BRAF was 1:4 (Bauer et al. 2007; Ichii-Nakato et al. 2006). As seen by these ratios, the greater the size of the nevus, the higher the probability of an NRAS compared to BRAF mutation.

Cell of Origin

Morphologically, congenital nevi are typically compound or intradermal. In larger nevi, the cells can extend quite deeply into the soft tissues, including the meninges and CNS. This is referred to as neurocutaneous melanosis. The probability of neurocutaneous melanosis is greatest in giant congenital nevi and particularly those involving the trunk with many satellite lesions. Clearly, UV stimulation does not play a role in these lesions, which occur in utero. The melanocyte of origin is probably most often of dermal origin, as these lesions morphologically are characterized by deep dermal extension between collagen fibers and tracing of adnexal structures. However, these morphologic features are not specific to congenital nevi and can be seen in nevi, which demographically and historically are clearly common acquired nevi. Again, the authors theorize that it is the dermal origin of this subset of common acquired nevi that causes this morphologic pattern.

Senescence and Other Factors Impacting Morphology

Congenital nevi may develop benign secondary clonal proliferations, which, if limited, are often referred to as clonal nevi and, if extensive and highly proliferative, may be referred to as benign proliferative nodules. These clonal proliferations are the result of additional mutagenic events, such as loss of function mutations in critical tumor suppressor genes. Morphologically, proliferative nodules can raise significant concern for melanoma because of significant cytologic atypia, mitotic activity, and clonal copy number aberrations. However, these copy number aberrations are typically whole chromosomal aberrations rather than segmental gains or losses, as seen in melanoma. Morphologically these secondary proliferations can vary, with possibilities that include Spitzoid, a variety of blue nevus subtypes (epithelioid, cellular conventional blue, or DPN-like), to spindle cell, epithelioid, or small round blue cell like appearances. This is likely dependent on the subsequent mutagenic events taking place.

The large size of some congenital nevi is unique and, of course, not seen in acquired nevi. Additionally, as previously discussed, only NRAS mutant melanocytic proliferations tend to reach the size of giant congenital nevi (Bauer et al. 2007). Oncogene-induced senescence in NRAS may be a more delayed process in comparison to BRAF. Additionally, because of the young age of the patient there may be more replications allowed before replicative senescence takes effect and perhaps, the relatively immunosuppressed state of pregnancy and the in utero child allows for less immune surveillance-mediated senescence. While the precise reason leading to the ability of these nevi to reach such a large size is unknown, all of these factors could theoretically contribute to this process.

Melanoma Risk

The lifetime risk of melanoma in a congenital nevus is proportional to the size of the lesion, with giant congenital nevi having the greatest risk. In giant congenital nevi, the lifetime risk is approximately 5 to 10% with most cases occurring before age 18 (Ruiz-Maldonado et al. 1992; Bett 2005). Although controversial, there are several theoretical reasons to believe that congenital nevi have a higher risk to transform to melanoma than other nevi (Illig et al. 1985; Swerdlow et al. 1995; Rhodes et al. 1996). This includes more frequent NRAS mutations in comparison to BRAF mutations (Bauer et al. 2007; Kinsler et al. 2013). As discussed earlier, NRAS is upstream of BRAF, and activating mutations in NRAS can simultaneously activate both the MAP kinase and Phosphoinositol kinase pathways. Congenital nevi are usually present for longer periods of time than acquired nevi, and keeping in mind that even benign nevi are not static, in that melanocytic cells are undergoing ongoing death and replenishment over a lifetime, there is a higher probability for a secondary mutagenic event and more time to have potential UV exposure. Despite these theoretical reasons, the data suggest that if there is a greater risk for small congenital nevi, this is so small that it is difficult to quantify (Scalzo et al. 1997).

Blue Nevi

Definition

Blue nevi are one subtype of dermal melanocytosis. The term dermal melanocytosis refers to a proliferation of dermal melanocytes with predominantly dendritic cell morphology, often with many surrounding melanin-laden macrophages and devoid of a junctional component. The predominant presence of deeper melanin gives rise to the blue color. A discrete macule or papule with this morphologic pattern is referred to as a blue nevus. There are many subtypes of blue nevi, including epithelioid blue nevi, epithelioid blue nevus of chronically sun-damaged skin, cellular blue nevi, and plaque type blue nevus. Other patterns of dermal melanocytosis, which present more as a dermatomal patch or plaque of pigment, are referred to as "nevus of Ota" when involving the conjunctiva and periocular skin and "nevus of Ito" when involving the shoulder and upper back.

Newborns sometimes have faint blue patches of pigment on either the wrist, ankle, or buttocks region, colloquially referred to as "Mongolian spots."

Clinical and Histologic Presentation

Blue nevi may be congenital or acquired and occur most commonly on the dorsal wrist, dorsum of the feet, or in a head and neck distribution. They can occur in other organs other than the skin. In the CNS, they are referred to as melanocytomas. Most acquired blue nevi are clinically less than 1 cm in total diameter and have a uniform blue to blue-black color. Dermoscopic exam also reveals a uniform blue pigment. Histologic exam shows dendritic melanocytes and melanophages often in a somewhat sclerotic stroma (Fig. 5). Segmental distributions, if highly cellular, may be referred to as plaque type blue nevi, whereas less cellular segmental distributions around the orbit are referred to as "Nevus of Ota" and around the shoulder as "Nevus of Ito."

Epithelioid blue nevi have, in addition to the dendritic melanocytes, a majority of melanocytes which also maintain deep prominent melanin pigmentation but with an epithelioid morphology. These lesions may occur sporadically or with increased incidence in patients with Carney's syndrome, which consists of lentigines, myxomas, and epithelioid blue nevi. Epithelioid blue nevi do not have distinguishable clinical features. Cellular blue nevi often have the dendritic

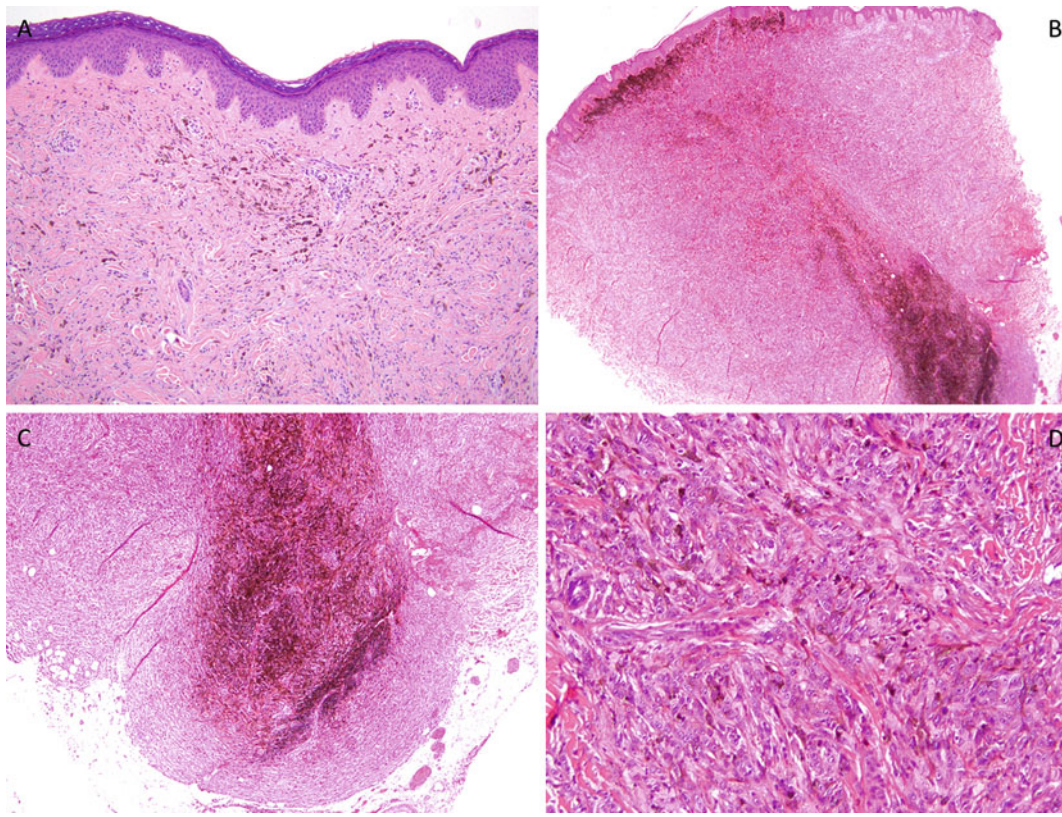

Fig. 5 (**a**) This image shows a dermal proliferation of dendritic and spindle shaped melanocytes in a fibrotic stroma with many intervening melanophages consistent with a conventional blue nevus. (**b**–**d**) The next images show a cellular blue nevus. The lower magnification shows the typical expansile cellular base which forms a buttress against the subcutaneous tissue. The highest power magnification shows fascicles of plump to oval spindle shaped melanocytes closely opposed to one another with only thin intervening strands of collagen.

melanocytic component but also have fascicles of oval to spindle-shaped cells, which often do not contain much melanin pigment, arranged in a plexiform pattern in the skin often forming a buttress against the subcutaneous tissue. Clinically, these lesions are typically raised, larger nodular lesions with a predilection for the cranio-sacral axis. Epithelioid and cellular blue nevi can often show benign involvement of lymph nodes.

Initiating Oncogenic Event

Activating mutations in the G-alpha Q family, GNAQ (65%) or GNA11 (9%), are seen in the majority of blue nevi (Van Raamsdonk et al. 2009). These genes encode for members of the q class of G protein alpha subunits and are involved in mediating signals between the G protein coupled receptors and downstream effectors which ultimately impact the MAP kinase pathway as in many of the other primary activating mutations in melanocytic neoplasms. The possible importance of the G-alpha Q family of proteins in blue nevi and other dermal melanocytosis was indicated by identifying hypomorphic germline mutations in these genes in a set of heavily pigmented mice (Van Raamsdonk et al. 2004). Histopathologic exam of these mice showed the same dendritic cell morphology of melanocytic proliferation as recognized in blue nevi and other dermal melanocytosis. It was not only shown that the majority of blue nevi have GNAQ or GNA11 mutations but that 46% of uveal melanomas do, as well (Van Raamsdonk et al. 2010). This is not surprising considering the overlapping morphology between the two entities. As is the case with most primary activating mutations, GNAQ and GNA11 mutations occur mutually exclusive of one another. Mutations in these genes either result in complete or partial loss of the protein's GTPase activity, leaving them constitutively activated. Epithelioid blue nevi result from a loss of heterozygosity in PRKAR1A in the context of an acquired nevus with a BRAF V600E mutation. This explains the increased incidence in Carney's complex, in which patients have a germline mutation in one copy of the PRKAR1A gene.

Cell of Origin

The distinctive common genetic alterations, histomorphology and lack of any epithelial involvement of blue nevi, dermal melanocytosis, and uveal melanoma have led to the proposal that they arise from a distinct type of melanocyte that does not reside within epithelia (Van Raamsdonk et al. 2010; Bastian 2014). These melanocytes are likely derived from the neural crest-derived bivalent precursor cell that can give rise to melanocytes and Schwann cells. These cells rely on endothelin signaling for differentiation and proliferation, which signals through the Gαq pathway, in which GNAQ and GNA11 operate. It is likely that these cells are the origin of blue nevi and their migration along the peripheral nerves explains their frequent presentation in sites such as the dorsal wrists and feet. Histologic exam often shows the dendritic melanocytes of blue nevus cells clustered around adventitia, such as hair follicles, which is also consistent with this theory of their origination. There are some tumors with composite features of blue nevi and various neural neoplasms, which have been designated as neurocristic hamartomas. The authors have personally noted some young children with composite tumors showing mixed differentiation, which include mixed morphologic and immunohistochemical staining patterns of blue nevi and neurofibromas. This further supports a similar derivation of blue nevus and Schwann cells.

Risk for Melanoma

Malignant transformation of dermal melanocytosis such as blue nevi, nevus of Ota, nevus of Ito, and Mongolian spots is uncommon, but may be no less frequent than in the much more common acquired nevi. It is difficult to estimate the incidence, as some of the largest case series of what has been referred to as malignant blue nevus or melanoma ex blue nevus typically include less than 20 cases (Connelly and Smith Jr. 1991; Costa et al. 2016) (Fig. 6). It is reasonable to conclude that malignant degeneration of these lesions undoubtedly happens but is a relatively rare

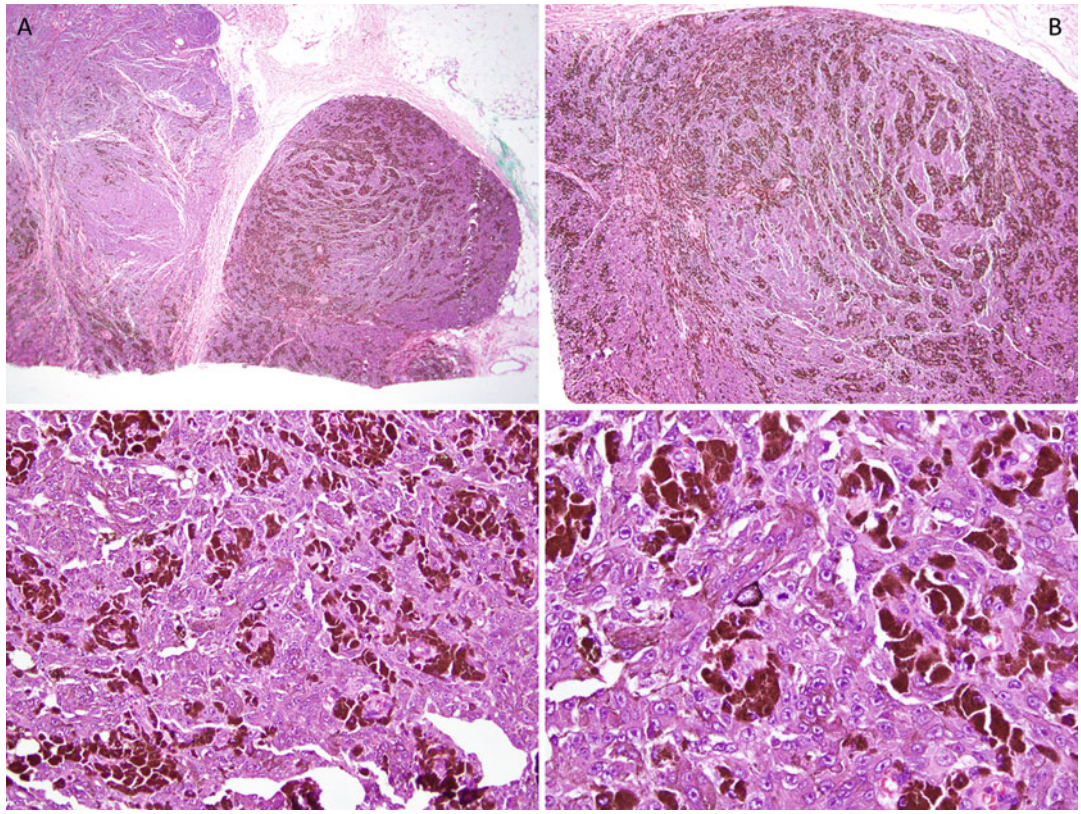

Fig. 6 (**a**) Low power view of a malignant blue nevus. Asymmetric expansile nodules of melanocytes with many melanophages abutting the subcutis. (**b**) While there are areas of residual conventional blue nevus in the background, this higher power magnification shows an area of epithelioid transformation. (**c** and **d**) At the highest magnification, one can see sheets of epithelioid melanocytes with notable nuclear atypia, prominent central nucleoli, and mitotic activity. Loss of BAP1 nuclear expression in these tumors has been shown to be an adverse prognostic parameter as in uveal melanoma.

event. Caucasian patients with nevus of Ota have an increased risk of uveal melanoma. When cutaneous melanoma occurs in these abovementioned lesions, they have similar genomic patterns and morphologic features to uveal melanoma, further underlining their close biologic relationship. It has long been recognized that the pattern of genomic alterations in uveal melanomas could be used to predict prognosis. Initially, this was done by cytogenetics. Cases with deletions involving 3p21 (BAP1) or gains/amplifications of 8q24 (c-Myc) had a significantly worse prognosis than cases without either of these alterations (Aalto et al. 2001; Harbour et al. 2010). More recently, it has been shown that while mutations in BAP1 are associated with aggressive disease, mutations in EIF1AX and SF3B1 may be good prognostic markers (Harbour and Chao 2014). Furthermore, not entirely surprisingly, in a recent study of cutaneous malignant blue nevi and cellular blue nevi, BAP1 mutations were similarly associated with aggressive disease, further establishing the similarities of melanomas arising from blue nevi and uveal melanoma (Costa et al. 2016).

Melanoma

Background Clinical and Histologic Features

The traditional classification of melanoma by Clark and colleagues distinguishes 4 major classes of cutaneous melanomas, which

includes superficial spreading type, nodular type, acral type, and lentigo maligna type. This classification system is primarily based on a combination of clinical and histomorphologic features.

Superficial Spreading Melanoma

Superficial spreading melanomas (SSM) are the most common subtype of melanoma accounting for approximately 60% of all melanomas (Singh et al. 2016). They may occur in all areas of the body but are most frequent on the trunk and extremities. This is the subtype of melanoma most likely to evolve from a precursor nevus and is the subtype of melanoma most linked to elevated nevus counts (Maldonado et al. 2003; Tsao et al. 2003). The ABCD rule is most useful and relevant to this subtype of melanoma. It suggests looking for asymmetric lesions, irregular borders, multiple colors, and size greater than 6 mm (Rigel et al. 2005). Common abnormal dermoscopic features include radial streaming, unilateral pseudopods, black blotches, and atypical network which are all features correlating to an atypical radial growth phase or in situ component. These lesions most often occur in areas of intermittently sun-damaged skin but can also occur in areas of chronic sun damage.

Histologically, these lesions are defined by having a radial growth phase with or without any vertical growth phase, but if there is a vertical growth phase, it is accompanied by an adjacent radial growth phase component that extends at least 3 rete ridges (by convention) beyond any vertical growth phase component. Prominent lentiginous growth of melanocytes along the dermal-epidermal junction with single melanocytes often predominating over nests is common. Lesions are often highly asymmetric and have poor lateral circumscription, often having irregular dispersion of single melanocytes at one lateral edge (Fig. 7). Pagetoid spread of melanocytes is common and may be widespread. Expansile junctional nesting with clustered mitoses and widespread nuclear atypia of melanocytes is commonly seen. A nevus remnant is present in up to one-third of cases.

Nodular Melanoma

Nodular melanomas may also occur both in areas of chronic and non-chronic/intermittently sun-damaged skin. A precursor nevus may be present but is less frequent than in the SSM subtype of melanoma (Pan et al. 2017; Yelamos et al. 2015b). Nodular melanomas are less likely to be identifiable by ABCD criteria. Lesions may be either symmetric, uniformly colored or asymmetric, multicolored nodular or papular lesions. Many cases are amelanotic and lack significant pigmentation and are often mistaken for basal or squamous cell carcinomas. There may be some dermoscopic clues, which include blue-white veil, multiple colors, the presence of shiny white streaks (Verzi et al. 2018), and a dot or polymorphous vascular pattern. While prognostically there is no difference between similarly staged SSM and NM, on average NM is diagnosed at a more advanced stage than SSM and is responsible for a disproportionate number of melanoma-related deaths (Mar et al. 2013). Studies suggest both the rapid growth of NM which goes directly into a vertical growth phase without a preceding radial growth phase and the difficulty in clinical recognition of these cases contributes to the advanced stage at diagnosis (Betti et al. 2008; Liu et al. 2008).

Histologically, nodular melanomas may have a junctional component, but they often do not have fully developed changes of melanoma in situ. By definition, if present, the junctional component does not extend more than 2 rete ridges beyond the dermal component. In NM the intraepidermal component may only have scattered signs of a more disconcerting process, such as focal areas of atypical junctional melanocytic hyperplasia, foci of pagetoid cells, or expansile nesting. In the dermis, there is often expansile nesting or sheet-like growth of melanocytes with nuclear atypia and mitotic activity. In histologic assessment of nodular melanomas arising from a nevus, melanocytes in the dermis often go through a transition, in which the cytology changes from that of a small, banal appearing cell with open chromatin and an unremarkable nucleolus to a large atypical cell with atypical nuclear features and a large prominent nucleolus with dusty,

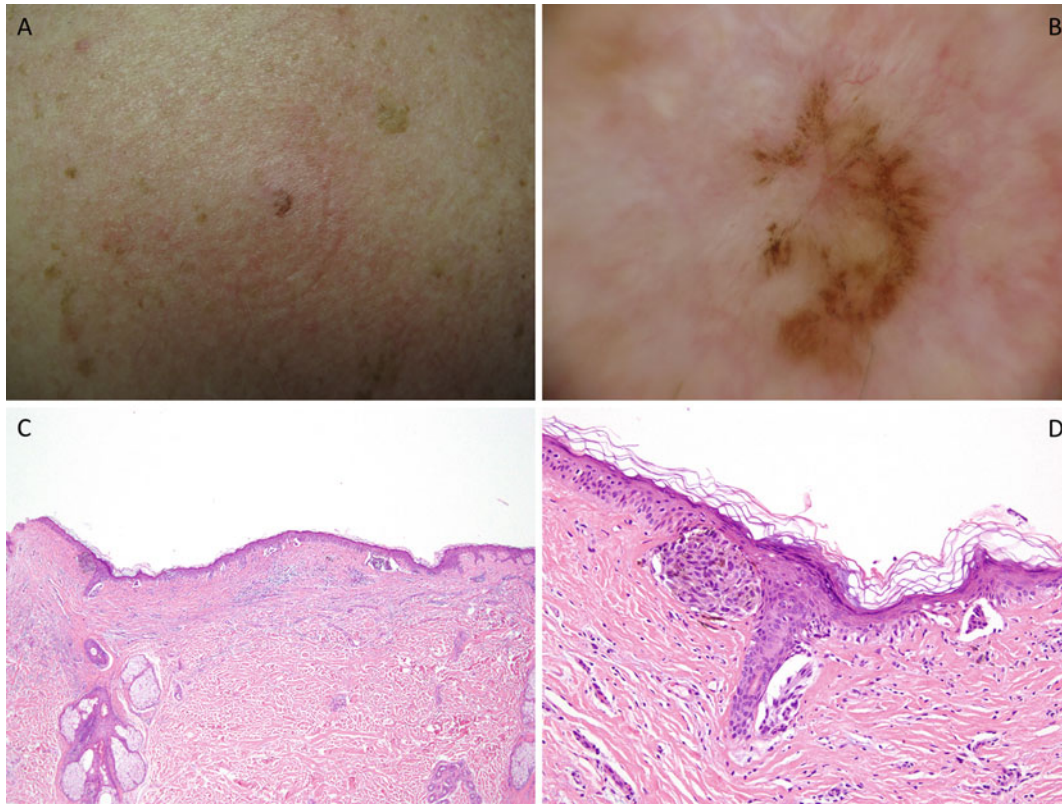

Fig. 7 (**a**) 65-year-old male with a new, irregular, multicolored macule measuring 5 mm on the back. (**b**) Dermoscopic assessment shows asymmetric streaks extending along the 1 o'clock to 5 o'clock edge. There are scar-like white areas consistent with regression, scattered asymmetric granules seen between 10 and 3 o'clock, and a focus of a residual distorted network around 6 o'clock. (**c**) Low power histology reveals an irregularly nested proliferation of highly atypical and pleomorphic melanocytes along the DEJ consistent with melanoma in situ and prominent underlying regression in the superficial dermis. (**d**) The higher magnification shows the irregularly nested atypical melanocytes with clefted spaces at the DEJ and broad underlying regression. This melanoma occurring on intermittently sun-damaged skin with a prominent nested pattern and highly pigmented melanocytes has a high likelihood of BRAF mutation.

pigmented cytoplasm. Even when an in situ melanoma component is present, it is unlikely that invasive melanoma always originates from the epidermis.

Lentigo Maligna Melanoma

Lentigo Maligna Melanoma (LMM) is a subtype of melanoma occurring exclusively in areas of chronically sun-damaged skin. Epidemiologically, melanomas of this type are most linked to lower intensity but prolonged and excessive UV exposure that results in the normal collagen bundles of the dermis developing into broad bands of grey solar elastotic material. They are predominantly seen in a head and neck distribution or on distal extremities and less commonly on the trunk. These melanomas often have a prolonged radial growth phase before entering a vertical growth phase. Lesions often appear as a variably pigmented patch on a background of poikilodermatous skin. Helpful dermoscopic features include asymmetric perifollicular pigmentation or perifollicular pigmented dots, rhomboidal structures or angulated lines, areas of homogeneous pigmentation, or essentially an asymmetric pigment blotch. In general, any

newly occurring melanocytic neoplasm occurring in a background of poikilodermatous/sun-damaged skin measuring 1 cm or greater in diameter should be considered highly suspicious for lentigo maligna.

The histologic growth pattern of LMM consists of single, variably atypical melanocytes, growing along the dermal-epidermal junction with less pagetoid spread than typically seen in superficial spreading melanomas. The epidermal rete ridges may or may not be effaced as a result of the extensive basal layer proliferation of atypical melanocytes. The lentiginous growth of single melanocytes may have florid extension into the adnexal epithelium (Fig. 8). A nevus remnant is not seen, but it is not uncommon to find small dermal nevic aggregates. These are not precursors but rather incidental benign nevi, as is commonly found in these anatomic sites. These melanomas are notorious for having a field effect as the direct result of mutagenic effects of ultraviolet exposure. This can result in melanocytic cells away from the primary focus carrying the same genetic alterations as those in the primary focus. Likewise, there can be skip lesions. Often, one may attempt a small incisional biopsy and find nondiagnostic changes. Clearance of these lesions can be difficult since areas of surrounding field effect can result in recurrences.

The dermal component may be a conventional epithelioid invasive melanoma or a desmoplastic spindle cell neurotropic melanoma. Desmoplastic spindle cell melanomas have hyperchromatic, atypical spindle shaped melanocytes often in a myxoid stroma with surrounding lymphoid aggregates, extending deep into the skin, often to or below the level of the subcutis. These hyperchromatic spindle cells may form fascicles deeply diving down into the dermis. There is often a sclerotic stroma, which pushes aside the solar elastosis, so that there is a rim of thick solar elastotic material around the periphery of the lesion. Neurotropism is common. Prognostic studies have shown that those cases with >90% desmoplastic pattern have low incidence of lymph node involvement, compared to cases that are more biphasic and have both a desmoplastic and solid epithelial component making up more than 10% of the lesion (Gyorki et al. 2003; Pawlik et al. 2006; George et al. 2009).

Acral Lentiginous Melanoma

Acral lentiginous melanoma (ALM) is a subtype of melanoma occurring on the volar surfaces of hands and feet and the nail apparatus. However, not all melanomas on acral surfaces are of the acral lentiginous subtype of melanoma. This subtype, like lentigo maligna, has a prominent radial growth phase component with single atypical cells along the dermal-epidermal junction. Importantly, because this subtype of melanoma has either limited or no UV signature mutations, UV exposure is not thought to be the predominant factor in most cases. More on acral melanomas is discussed in a separate chapter.

Initiating and Characteristic Oncogenic Events

Genomic changes resulting in malignant transformation of melanocytes is covered in detail in the ▶ Chap. 7, "Molecular Genetics of Melanocytic Neoplasia." In this section, we will focus on discussing the initiating genomic event most typical of each subclass of melanoma. There is not a perfect correlation of genomics with subtype or clinical and morphologic features, but there are some general trends. For example, factors such as younger age (<55 years of age) (Viros et al. 2008), involvement of skin without a high cumulative level of sun exposure (Broekaert et al. 2010), the presence of a precursor nevus, nest formation, notable melanin pigmentation, and a radial growth phase with notable pagetoid scatter have all been linked to higher likelihood of a BRAF mutation. These given clinical and morphologic features are most typical of the superficial spreading type of melanoma, and hence it follows that superficial spreading melanomas are the most likely type of melanoma among the 4 subtypes to have a BRAF mutation as the initiating genomic event. Approximately 52% of

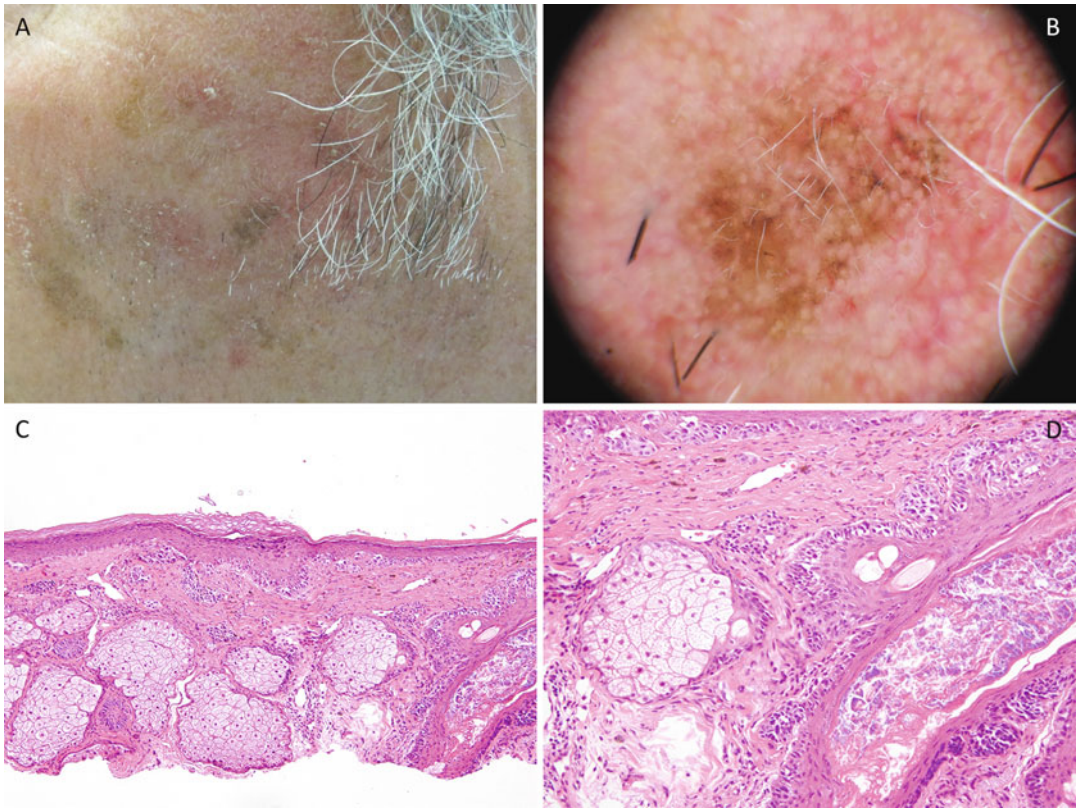

Fig. 8 (**a**) Poikilodermatous skin with a brown pigmented patch anterior to the sideburn in a 72-year-old male. (**b**) Dermoscopic assessment shows a pseudoreticulated pattern and the presence of asymmetric clusters of pigment granules in a perifollicular distribution, a feature often seen in lentigo maligna. (**c**) Low power histology of a lentigo maligna type of melanoma, which shows broad lentiginous growth of single melanocytes with small nests predominantly in the basal layer of the epidermis and within the follicular epithelium. (**d**) The higher magnification highlights the confluent single cell proliferation of atypical melanocytes in the follicular epithelium. This pattern of broad single cell growth of atypical melanocytes above chronically sun-damaged skin can be seen in KIT mutated melanomas. The melanocyte precursor in this case is an epithelial-derived melanocyte and likely has a high mutational burden.

SSM have BRAF and 20% have NRAS mutations (Viros et al. 2008).

The genomics of nodular melanomas may vary considerably, depending on whether they are nodular melanomas occurring in an area of the skin with high, low, or no cumulative sun exposure. Again younger age, location in areas of intermittently sun-damaged skin, and the presence of a precursor nevus increase the likelihood of a BRAF mutation. Conversely, the probability of an NRAS mutated NM increases with older age (Ellerhorst et al. 2011). The frequency of BRAF mutations in nodular melanomas in general is 41% and of NRAS is 27% (Lee et al. 2011). Another characteristic genomic alteration in amelanotic nodular melanomas is copy number gains in 8q24 at the C-Myc locus (Pouryazdanparast et al. 2012a; b). There is evidence that elevation in Myc can down regulate MITF, which is the master regulatory gene of pigmentary production. This results in decreased levels of tyrosinase, decreased melanin production, and an amelanotic appearance.

The initiating oncogenic event in LMM may involve NF1, c-Kit, NRAS, or BRAF. NF1 mutations are particularly common in those LMM

cases with a desmoplastic and spindle cell component (Gutzmer et al. 2000). Mutations in c-Kit can be seen in approximately 20% of melanomas of LMM and are most typical of those melanomas which begin with a broad lentiginous growth pattern along the dermal-epidermal junction (Curtin et al. 2006). Approximately 22% of LMM have BRAF mutations and 14% of LMM have NRAS mutations.

Approximately 20% of ALM have BRAF mutations, 30% have NRAS mutations (Haugh et al. 2018), 20% have c-KIT mutations (Curtin et al. 2006), and 17% have NF1 mutations (Moon et al. 2018). Structural aberrations with copy number gains in Cyclin D1 and CDK4 as well as deletions in CDKN2A are also particularly common in this subtype of melanoma (Bastian et al. 2000).

BRAF and NRAS mutations alone are insufficient for malignant transformation of melanocytes, and these mutations can be seen in nevi as well. It is the accumulation of additional genomic events over time, typically the result of UV exposure that results in the transformation of these lesions to melanoma (Shain et al. 2015). Some critical additional genomic events leading towards transformation with an initiating activating mutation in BRAF or NRAS include subsequent TERT promoter mutation or amplification, homozygous deletion or mutation in CDKN2A, or PTEN deletions or mutations (Tsao et al. 2004; Dankort et al. 2009; Huang et al. 2013). In ALM, which mostly occur independent of UV damage, structural aberrations in chromosomes leading to copy number gains in oncogenes or deletions of tumor suppressor genes have a greater role.

Cell of Origin

Superficial spreading, acral lentiginous, and lentigo maligna melanoma all likely originate from an epidermal-derived melanocyte as evidenced by the characteristic radial growth phase component seen in these tumors. The nodular types of melanoma may occur via an epidermal-derived melanocytic cell, which may explain the majority of nodular melanomas. However, some nodular melanomas have no junctional component and may evolve through a dermal derived melanocytic cell. In the author's experience, many nodular melanomas evolve from a conventional compound or dermal nevus. Hence, if the original nevus is compound and derived from an epidermal melanocyte, the subsequent melanoma would also be. Contrastingly, a melanoma arising from a dermal nevus with congenital features likely is originating from a melanocytic cell of dermal origin. Desmoplastic spindle cell melanomas which only have an overlying lentiginous melanoma in the epidermis in 50% of cases may originate from UV damage to a dermal melanocyte. Transformation of a dermal melanocyte having common origins with Schwann cells may explain the neural differentiation and neurotropism often seen in desmoplastic and spindle cell melanomas in chronically sun-damaged skin.

TCGA Classification

As described above, there is considerable genetic variability within the melanoma subtypes defined by Clark. With the emergence of genetic studies and recognition of important therapeutic implications of specific genetic aberrations in melanoma, other classification schemes have evolved. The TCGA of cutaneous melanomas excludes acral and mucosal melanoma and proposes a genetically based classification system which categorizes melanoma into four major groups: (1) BRAF mutated, (2) NRAS mutated, (3) NF1 mutated, and (4) triple wild type (i.e., wild type for BRAF, NRAS, and NF1). The last category is very heterogeneous and includes cases with c-KIT or GNAQ as well as other mutations and melanomas resulting from fusions or other structural aberrations. In the TCGA study, BRAF mutations were associated with younger age as in previous studies, as well as MITF amplifications. RAS mutations characteristically show elevated MAPK activation and AKT3 overexpression, while NF1 mutated melanomas were seen in older patients with higher mutational burden (Cancer Genome Atlas 2015).

An Integrated Taxonomy of Melanocytic Neoplasia

A taxonomy that integrates the clinical and histopathological features, genetic alterations, role of UV radiation, and epidemiological variation has been suggested by Bastian. This system classifies melanocytic neoplasms into two major categories: melanomas originating from melanocytes associated or not associated with epithelia such as epidermis or mucosa. Within each category, the classification distinguishes several classes of neoplasms that evolve from different types of precursor lesions to different melanoma subtypes through the progressive accumulation of genetic alterations (Bastian 2014).

The family originating from epithelia-associated melanocytes includes the following groups: (1) melanomas on sun-exposed skin without cumulative sun-induced damage (low-CSD melanomas) (Table 3). These melanomas lack marked solar elastosis in their surrounding skin, have frequent BRAF V600E mutations, and often arise from precursor nevi and affect the trunk and proximal extremities of patients under 55 years of age. (2) Melanomas on sun-exposed skin with high cumulative sun-induced damage (high-CSD melanomas). These melanomas show marked solar elastosis in their surrounding skin, have frequent NF1, NRAS, BRAF non-V600E, and KIT mutations, do not arise from precursor nevi, and affect the head and neck areas of patients over 55 years of age (3) acral melanoma, (4) mucosal melanoma, (5) desmoplastic melanoma, (6) Spitz melanoma, defined by specific genetic alterations such as HRAS mutation or kinase fusions. This

Table 3 Comparison of CSD and non-CSD melanoma

	Melanoma of non-CSD skin	Melanoma of CSD skin
Age at diagnosis (peak range)	40–50 years	60–80 years
Common sites of occurrence	Trunk and extremities or areas with intermittent bursts of UV exposure	Head and neck region or areas with prolonged and excessive UV exposure
Clinical presentation	ABCD rule – Most related to superficial spreading type of melanoma; lesions typically present with asymmetry, irregular borders, variegated color, and a diameter > 6 mm; often arise from a precursor nevus Nodular melanomas appear as either amelanotic or darkly pigmented, pedunculated, or polypoid nodules	Lentigo maligna melanoma often appears as a multicolored or darkly pigmented macular patch with variable pigmentation on a background of poikilodermatous skin Melanomas of SSM or nodular types appear similarly to those of non-CSD
Dermoscopic features	Typically include asymmetric blue-gray veil, unilateral pseudopods, radial streaming, irregular blue/black blotches and/or granules, shiny white streaks, or an atypical network; may also include dot or polymorphous vascular patterns	Typically include asymmetric perifollicular pigmentation, perifollicular pigmented dots, rhomboidal structures or angulated line, areas of homogeneous pigmentation
Histological characteristics	SSM – Broad radial growth phase extending at least three rete ridges beyond the dermal component; often single cells with lentiginous or pagetoid growth pattern predominating over nests Nodular – Lack a radial growth phase; have expansile nests or sheets of atypical mitotically active melanocytes in the dermis	Dermis has thick bundles of gray solar elastotic material LMM – Typically has a prominent basal layer proliferation of variably atypical melanocytes and an effacement of the rete ridge often with extensive involvement of the adnexa SSM and nodular possess similar characteristics to non-CSD melanoma
Common initiating genetic events	BRAF (50%) NRAS (30%)	NF1 (45% Desmoplastic melanoma) KIT (20%) NRAS (20%) BRAF (10–30%)

differs from Spitzoid melanoma, which is defined only by morphology, and has been shown to consist mostly of other melanomas (low-CSD) (cite PMID: 28186096).

The second category of melanocytic neoplasms arising from melanocytes not associated with epithelia consists of uveal melanoma, blue nevi and blue nevus-like melanomas, and melanocytomas of internal organs and related melanomas. These neoplasms are characterized by somatic mutations of the Gαq pathway, mostly at the level of GNAQ or GNA11. Also in this category fall bona fide congenital nevi and melanomas developing within leptomeninges. This classification system provides a more detailed subtyping of melanoma into groups that have greater homogeneity in underlying genetics and clinical behavior.

Staging of Melanoma

The American Joint Committee on Cancer has recently released the 8th edition of a Tumor, Nodes, Metastasis (TNM) staging system which includes specific changes to the T staging of melanoma. The primary factor in T staging is Breslow depth, which is a measurement from the granular layer of the epidermis to the deepest melanoma cell in the skin. Additional factors impacting the T stage include the presence of ulceration of the epidermis, which must be ulceration induced by excessive proliferation of melanoma cells near the surface of the skin and obviously does not include traumatically induced ulcers. Although in practice, it is not always simple to make this distinction. Mitotic count has been removed from the staging of T1 tumors. There is strong evidence in the literature linking mitotic activity to prognosis in general (Azzola et al. 2003; Francken et al. 2004; Thompson et al. 2011). However, the inclusion of mitoses as in the 7th edition as a discrete variable of absent or present was suboptimal. Numerous studies have also shown that the hot spot method of counting mitoses has considerable interobserver variability (Larsen et al. 1980; Heenan et al. 1984; Cook et al. 1996). Eventually, when more optimal cut off parameters for mitoses can be identified, it is likely that mitotic count will be re-introduced into the AJCC staging system.

In the 8th edition, T1a tumors are those that <0.8 mm in Breslow depth without ulceration. Tumors that are 0.8–1.00 mm with or without ulceration are T1b. Tumors ranging from >1.0 mm to 2.00 are T2, from >2.0 to 4.00 are T3, and those tumors greater than 4.00 mm are T4. The presence of ulceration moves the staging from T2a, T3a, or T4a to T2b, T3b, or T4b, respectively. According to the AJCC database of 23,001 patients stratified for T stage with no evidence of regional or distant metastasis at the time of diagnosis, the 10-year melanoma-specific survival was 98% for T1a, 96% for T1b, 92% for T2a, 88% for T2b, 88% for T3a, 81% for T3b, 83% for T4a, and 75% for T4b (Gershenwald et al. 2017.

The TNM classification of melanoma has contributed significantly to the ability to provide patients prognostic information about their disease, guide management, and standardize clinical trials. However, there remains a significant proportion of early stage patients who develop aggressive disease and patients with more advanced T stages including some with microscopic lymph node involvement who do well (Shaikh et al. 2016; Whiteman et al. 2015; Landow et al. 2017). Hence, there are limitations to traditional morphologic descriptors. Recently, a molecular-based staging system assessing mRNA expression of 31 distinct genes has emerged in clinical practice in the United States (Gerami et al. 2015a, b; Zager et al. 2018). This molecular test classifies melanoma into four categories: class 1a, 1b, 2a, and 2b and in retrospective studies has shown highly statistically significant correlation with outcome in multivariate analysis, independent of traditional prognostic markers.

Conclusion

In conclusion, this chapter describes the clinical and histologic features of melanoma and their relationship to the more recently described genomic alterations. Genetic changes are becoming increasingly important to assist in the diagnostic

classification of ambiguous melanocytic neoplasms. An example of this could be identifying a GNAQ mutation in a spindle and dendritic shaped melanocytic neoplasm with some atypia, which would favor blue nevus over the differential diagnosis of a desmoplastic melanoma. In malignant melanocytic neoplasms, the classification system is useful in predicting the pretest probability of finding genetic alterations predictive of response to targeted therapy. These are just two examples of how a classification system integrating genomics and melanocyte biology, as outlined in this chapter, could be utilized to better diagnose and predict the behavior of melanocytic neoplasms of the skin.

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