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Principles for Melanoma Diagnosis Learned From the Study of Nevi in Children (SONIC)

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Cutaneous melanoma is a potentially lethal disease that offers a unique chance for early detection and cure like no other cancer. The late Bernard Ackerman, MD, spelled out the goal of early melanoma detection succinctly in his aptly titled 1985 paper, "No One Should Die of Malignant Melanoma."[1]

To achieve early detection, clinicians have proposed multiple clinical strategies, including the ABCDE early recognition criteria [A (asymmetry), B (border irregularity), C (color variegation), D (diameter >6 mm), E ("evolving")[2]] and the "ugly duckling" sign. The latter highlights that melanoma can be an outlier lesion, differing in size, color and pattern from the patient's benign nevi, which often appear similar to one another.[3]

Physicians have also improved diagnostic accuracy by incorporating imaging technologies in clinical practice. Dermoscopy enables evaluation, at higher magnification, of subsurface patterns and structures that are not visible to the naked eye; dermoscopic digital monitoring allows short-term follow-up of the dermoscopic pattern of melanocytic lesions for stability versus change over time. Total-body photography also assists in long-term monitoring, whereby a melanoma can be detected as a new or changing lesion among the patient's host of stable benign nevi.

Despite all these diagnostic techniques, some melanomas elude diagnosis; not only very early or small-diameter melanomas, but also nodular, amelanotic and nevoid melanomas, as well as those arising on sun-damaged skin. Difficult-to-diagnose melanomas need to be differentiated from the patient's benign

Continued on page 2

IN THIS ISSUE:

Principles for Melanoma Diagnosis Learned From the Study of Nevi in Children (SONIC)

Clinical and Dermoscopic Morphology in Diagnosis of Melanoma in Childhood

Treatment of Pediatric Melanoma

From the Editors

Much has happened in the diagnosis and treatment of pediatric melanoma in the decade since we last covered the topic in depth in *The Melanoma Letter*. In this issue, six excellent contributors update us on advances in our understanding of the evolution of nevi in childhood, the use of dermoscopy in the diagnosis of pediatric melanoma and the application of the new exciting therapies for advanced metastatic melanoma in this age group.

In his lead story, Alon Scope, MD, reminds us of the well-established early recognition tools such as the ABCDEs of melanoma and the "ugly duckling" technique, also emphasizing the benefits of dermoscopic digital monitoring and total-body photography as aids to diagnosis. He elaborates on the lessons learned from the

Continued on page 10

Continued from page 1

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nevi. In such scenarios, physicians may glean subtle diagnostic clues from the clinical context, taking into account different patient-related factors.[4]

For the most part, a patient's nevi abide by "rules" — their morphology and biological behavior depend on the patient's demographic, phenotypic, genetic and environmental factors. If we decipher these rules that govern the morphology of nevi, we may be able to detect an otherwise difficult-to-diagnose melanoma that is breaking these rules.

The Importance of Childhood Nevi

Melanocytic nevi are a strong phenotypic marker of cutaneous melanoma risk.[5] Nevi frequently develop in the first two decades of life, making this a prime period for studying when, where and how nevi should appear. The Study of Nevi in Children (SONIC), a population-based study centered in Framingham, Massachusetts, has documented the morphology of nevi and their evolution over time during childhood and adolescence. We accrued participants at ages 11 to 14 from all schools in the Framingham district and followed a subset of their nevi, using clinical and dermoscopic imaging, until age 17. By administering questionnaires to participants and their parents and conducting on-site skin examinations, we collected demographic, clinical, phenotypic and environmental exposure data.[6]

Here, we offer examples of nevus rules that we established from the SONIC project and from other studies of nevi, and the implications for detecting a melanoma that is breaking these rules.[7] Obviously, there are exceptions; not every lesion that deviates from the expected pattern is an obligatory melanoma. Nonetheless, a deviant lesion should be approached judiciously to exclude melanoma.

Rule: The pattern of nevi depends on the patient's age

Multiple studies have shown a major shift in the predominant dermoscopic pattern of nevi from childhood to adulthood.[8] The most frequent dermoscopic nevus pattern in children is the globular type (**Figure 1A**), and the most frequent pattern in adults is the reticular type (**Figure 1B**). In the SONIC cohort, at age 11, 34 percent of back nevi were globular, while only 11 percent were reticular.[9] During follow-up from age 11 to age 17, we observed a gradual decline in the percentage of globular nevi and an increase in that of reticular nevi. This pattern shift was not due to change within individual nevi, but the appearance of more nevi with reticular patterns; at age 17, of new back nevi, 44 percent were reticular and only 16 percent were globular (unpublished data). This globular to reticular pattern shift continues into adulthood; in patients in their fourth decade, 61 percent of trunk nevi were reticular, while only 20 percent were globular.[8]

Another dermoscopic pattern of nevi that is highly age-dependent is the "peripheral rim of globules" (PRG) pattern (**Figure 1E**); this pattern signifies a growing nevus.[10] When the nevus ceases to grow, the peripheral rim of globules disappears and the nevus assumes one of the other patterns (e.g., reticular pattern). In the second decade, PRG nevi were observed in 3 percent of back nevi among SONIC participants[10] and in 5 percent of trunk nevi among adolescent patients visiting pigmented lesion clinics.[8] Notably, the frequency of PRG pattern rapidly declines

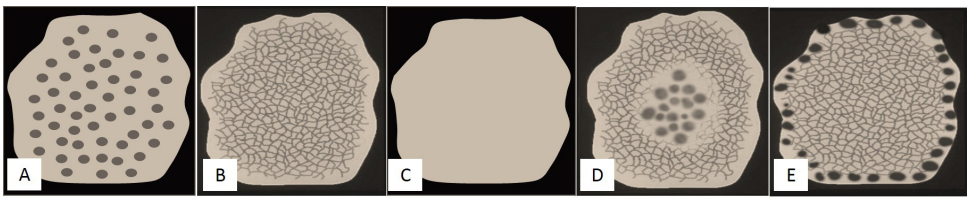

Figure 1. Common dermoscopic patterns of nevi.

(A) Globular pattern, (B) Reticular pattern, (C) Homogeneous/Structureless pattern, (D) Complex (reticular-globular) pattern, (E) Growing nevus with peripheral rim of globules (PRG) pattern.

with age — these lesions are seen in 1.5 percent of trunk nevi in the fourth decade, and in <1 percent of patients >50 years old.[8]

Significance for melanoma diagnosis

A new nevus with a globular dermoscopic pattern in an elderly patient is uncommon. Notably, a recently described subtype of melanoma termed "nested melanoma of the elderly"[11] can be recognized as a lesion with a diffuse globular pattern appearing in a patient at the "wrong age." Furthermore, melanomas that display a predominantly globular dermoscopic pattern have been shown to grow faster than melanomas that show a predominantly reticular pattern.[12] Finally, pigmented lesions that show a PRG pattern in a patient >50 years old should raise suspicion for melanoma.

Rule: The pattern of nevi depends on body site

In SONIC, we observed that the size and dermoscopic pattern of nevi depends on the anatomic site of the nevi.[6,13] First, nevi on the upper trunk tend to be larger in diameter and show a globular dermoscopic pattern (**Figure 2A**), whereas nevi on the lower trunk and extremities become increasingly smaller and tend to be more frequently reticular in dermoscopic pattern (**Figure 2B**). Second, nevi with a PRG pattern are very rare on the legs. Third, nevi with a complex dermoscopic pattern (**Figure 1D**), showing both globular and reticular components, occur more frequently on the trunk than on the extremities (**Figure 2C**).

Some exceptions exist; for example, a congenital ("birthmark") nevus that is located on the lower extremities may be the patient's largest mole; patients with the so-called "atypical nevus phenotype," who have a high nevus count and large nevi (>5 mm in diameter), may show nevi with a complex pattern on the extremities as well as on the trunk.

Significance for melanoma diagnosis

(**Figures 3A-3B**): An example of a suspect lesion breaking the anatomic site rules would be an acquired, singular pigmented lesion on the lower extremities of an adult that is larger in diameter than the patient's trunk nevi, and/or shows a globular, complex or PRG dermoscopic pattern.

Rule: The pattern of nevi depends on the patient's skin color

In SONIC and in other studies, a predictable association has been observed between a patient's skin color and the dermoscopic pattern and size of nevi.[6,14] Participants with darker skin tend to have nevi that are smaller in diameter and reticular in dermoscopic pattern; in contrast, participants with fair skin more frequently harbor larger nevi with a globular or complex dermoscopic pattern. Another subset of nevi are those that lack a specific dermoscopic pattern (termed "structureless" or "homogeneous" nevi, **Figure 1C**): Structureless, light-colored nevi are more frequent among fair-skinned participants. Skin color has been associated with germline variations in the gene for melanocortin-1 receptor (MC1R); indeed, individuals who harbor a mutation in MC1R, which is associated with fair phenotype and red hair color, show structureless nevi more frequently, whereas those with

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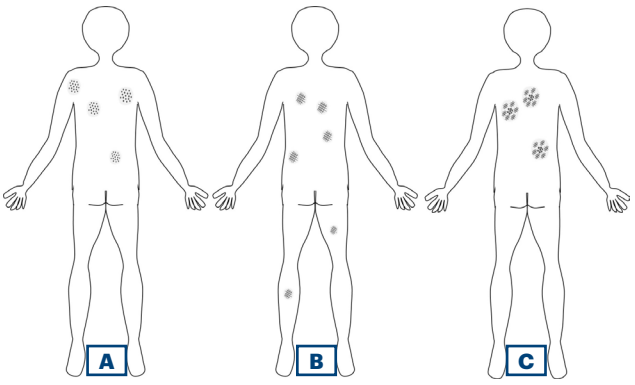

Figure 2. Dermoscopic pattern of nevi by body site.

A) Globular nevi are more prevalent on the torso, particularly on the upper back, where they tend to be larger and more numerous than globular nevi on the lower back. On the lower extremities, globular nevi are uncommon. Globular nevi are the dominant pattern in children.

B) Reticular nevi are the dominant pattern in adults and can be seen both on the torso and on the extremities. They are mostly smaller in diameter than globular or complex nevi.

C) Complex pattern nevi are seen more frequently in adults with a high nevus count that includes large nevi (the so-called "atypical mole phenotype"). Complex nevi are more common on the torso and infrequent on the lower extremities.

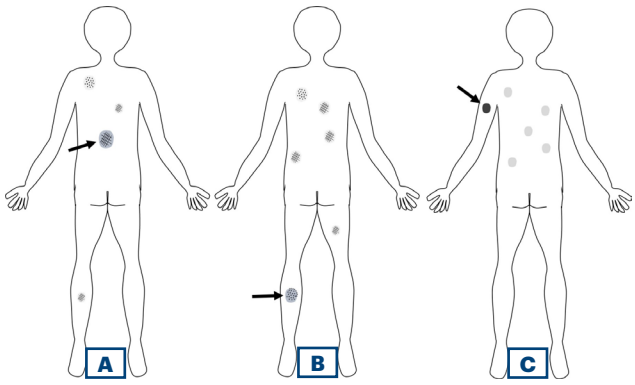

Figure 3. Melanomas that "break the rules."

A) The lesion with reticular pattern on the lower back (arrow) is larger than the patient's other upper back nevi, including the globular nevi. This lesion is breaking the size gradient — upper trunk nevi >lower trunk nevi and globular >reticular; if it is an acquired lesion in an adult, it should raise suspicion for melanoma. At times, melanomas arising on sun-damaged skin may present in this manner.

B) A globular lesion on the leg (arrow) of an older individual without a history of long-standing stability is suspicious for melanoma. New globular nevi are more likely to be observed in children and adolescents, and their frequency decreases in adulthood. Nevi on the lower extremities are more likely to be reticular than globular.

C) This patient has a light pigmentary phenotype with multiple light-colored (fair to light brown) nevi. The melanoma (arrow) is an acquired lesion that is too dark for the patient's skin type.

Clinical and Dermoscopic Morphology In Diagnosis of Melanoma in Childhood

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Melanoma diagnosed during childhood and adolescence is extremely rare, accounting for 1 to 3 percent of all pediatric cancers and 1 to 4 percent of all melanomas. Incidence increases tenfold after puberty, with one case per 100,000 in those 15 to 19 years of age (updated SEER).[1] Although this figure is extremely low, consultations regarding nevi account for 30 percent of visits to pediatric dermatologists.[2] This is likely because new and changing nevi are common in young people.

The dynamic nature of nevi during youth partly explains why more than 2 million mole biopsies were performed in patients under age 19 between 2009 and 2013 in the U.S., though only 1,940 melanomas were diagnosed: That's about 1,030 biopsies for every melanoma found.[3] Unfortunately, even with this high biopsy ratio, pediatric melanoma diagnoses are delayed longer than 12 months in more than 60 percent of cases.[4] Improved understanding of the clinical and dermoscopic morphology of these melanomas may allow timelier detection of these cancers while also eliminating many unnecessary nevus biopsies.

Three Categories of Childhood Melanoma

Based on clinicopathologic and molecular profiles, childhood melanomas can be classified into three broad catagories:[5] 1) melanoma arising in the context of large congenital nevi, 2) spitzoid melanoma (SM) and 3) conventional melanoma (CM) (i.e., superficial spreading or nodular melanoma). We present key features and comparisons of each of these categories in **Table 1**.[6]

Even with the use of dermoscopy, early diagnosis of melanoma arising in large congenital melanocytic nevi remains challenging since most of these melanomas arise from deep within the nevi, often within the deep dermis. However, early diagnosis of CM and SM can be facilitated via recognition of these lesions' clinical and dermoscopic features.[7] CM in children display the classic melanoma-specific structures described for superficial spreading and nodular melanomas. Hence, these melanomas are relatively easy to detect via dermoscopy. Dermoscopy of CM often reveals an asymmetric multicomponent pattern, with the lesion displaying melanoma-specific structures such as atypical or negative network, pseudopods/streaks, shiny white structures, blue-white veil, peppering, polymorphous vessels, blue-black color and irregular blotches.

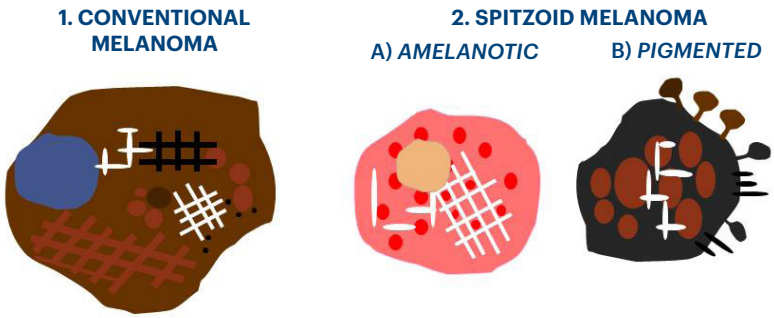
SM are a bit more challenging to diagnose. They usually present as fast-growing symmetric pink papules, often initially misdiagnosed as warts, dermatofibromas or vascular lesions. However, dermoscopy has helped to correctly identify these tumors. SM characteristically present with one of two patterns: 1) a starburst pattern in a heavily pigmented lesion or 2) a nonpigmented pattern with atypical vascular structures in a symmetric pink papule. Both patterns can also reveal shiny white structures on polarized dermoscopy. Thus, any symmetric lesion manifesting streaks, blue or black color, shiny white structures or polymorphous vascular structures should be viewed with suspicion and biopsied.

Even when we know the clinical and dermoscopic morphology, immunohistochemistry and molecular signatures of spitzoid neoplasms, we cannot confidently classify some atypical spitzoid tumors as benign or malignant since their biologic potential remains unknown. In such cases, the most prudent management approach remains complete surgical removal of the lesion.[8,9]

In conclusion, awareness of the clinical and dermoscopic morphology of pediatric melanoma can help avoid delays in diagnosis and reduce the high burden of excisions of banal nevi in children.

Figure 1. Schematics of the most frequent dermoscopic presentation of pediatric melanomas

1. *Conventional melanoma*: asymmetric pigmented lesion on the trunk, arising in a preexisting nevus showing multicomponent pattern (combination of network, globules and homogeneous areas) and/or the presence of any melanoma-specific features: atypical network, negative network, irregular globules/dots, blue-white veil, shiny white structures, atypical vessels or regression/peppering, in an otherwise symmetric nevus-like lesion (especially in early stages).



2. *Spitzoid melanoma*: de novo fast-growing lesion, mainly on limbs or head:

A) *Amelanotic pattern*: nonpigmented, symmetric papule or bump, showing atypical vessels (mainly dotted or milky-red areas), frequently with ulceration and shiny white structures or negative network.

B) *Pigmented pattern* (reed-like pattern): heavily pigmented papule or patch with the atypical starburst pattern: asymmetric peripheral streaks/pseudopods, shiny white structures, atypical black globules.

Table 1. Summary of Melanoma Subtypes in Children and Adolescents

	Conventional melanoma	Spitzoid melanoma	Melanoma arising in large congenital melanocytic nevi
Age	Most common in postpuberty	Any age	Most common in prepuberty
Race-phenotype	Fair skin/hair/eyes Nevus-prone phenotype	Any kind	+ Large CMN
Patient genetic background	Family or personal MM history (CDKN2A)	Unknown	Unknown
Natural history	Nevus-like or arising in a nevus	Pink fast-growing papule	Lesion arising within the LG-CMN or in central nervous system (CNS)
Location most common	Trunk	Limbs and head	Any location (skin or CNS)
Clinical appearance	**Classical ABCD:** • **Asymmetry** • **Borders irregular** • **Color uneven** • **Diameter >6 mm**	**Modified ABCD:** • **Amelanotic** • **Bump-bleeding** • **Color uniformity** • **De novo**	Any kind: skin or neuromeningeal MM (+/- neuromeningeal melanocytosis in MRI)
Dermoscopic patterns	• Multicomponent with classic melanoma features	• Pink vascular spitzoid • Pigmented spitzoid (atypical starburst)	• Classic MM features • Blue homogeneous or not applicable if dermal/subcutaneous MM • Not applicable if neuromeningeal MM
Histopathology of melanoma	Arising in a nevus (60%) ~ 70% invasive	De novo spitzoid MM ~ 100% invasive	Arising in LGCMN (100%) Dermal or neuromeningeal
Tumor genetic background	UVR damage signature BRAF-MAPK, TERT and PTEN pathways	ALK-fusions and other kinase fusions (not BRAF)	NRAS mutations

Abbreviations: CMN: congenital melanocytic nevus; LGCMN: large-giant congenital melanocytic nevus; CNS: central neural system; MM: melanoma; MRI: magnetic resonance imaging, UVR: ultraviolet radiation.

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Continued from page 3

MC1R variants associated with darker skin type tend to show nevi with a reticular pattern.[15]

Significance for melanoma diagnosis

An outlier, darkly pigmented lesion in an individual with a fair-skinned phenotype should raise suspicion for melanoma (**Figure 3C**). In addition, individuals with very fair skin, particularly those with an MC1R mutation associated with red hair color, may pose a particular challenge for melanoma diagnosis.[16] While their nevi tend to appear lightly pigmented and structureless under dermoscopy, a melanoma in such a patient may also lack pigment (termed "amelanotic melanoma") and display a structureless dermoscopic pattern. Hence, these very fair patients may benefit from closer surveillance using total-body photography to detect melanoma as a new or changing lesion.

Rule: Change in nevi is frequent in childhood

Among SONIC participants, we frequently saw newly appearing, changing and disappearing nevi.[9,17] Between ages 11 and 14, 75 percent of participants developed new nevi, while 28 percent had at least one nevus that disappeared. Of the new nevi detected at age 14, only half were stable over the next three years, while 43 percent increased in size and 5 percent disappeared. Disappearing nevi often gradually faded in color and/or shrank in diameter. Children with the highest baseline nevus counts were also those with the highest nevus volatility, i.e., with a proclivity for new, changing and disappearing nevi. We also observed that among children with many nevi, a history of sunburn could be associated with a greater increase in number of nevi.[15]

Significance for melanoma diagnosis

Use of total-body photography in children and adolescents to identify suspicious lesions based on change is likely to have poor specificity for the diagnosis of melanoma. The infrequency of melanoma, taken together with the high nevus volatility in the first two decades of life, make the use of total-body photography a less effective strategy for melanoma detection than in adults.

"A comprehensive understanding of the rules by which nevi abide may help in the early detection of melanomas that break these rules."

Rule: Melanoma risk is related to the patient's nevus phenotype

Having numerous nevi and large nevi (>5 mm in diameter) is associated with a high-risk phenotype for developing melanoma.[5] In SONIC, we found that children harboring more nevi than their peers at age 14 were those most likely to develop a high-risk nevus phenotype at age 17.[18] Individuals whose nevi showed greater variability in dermoscopic patterns (i.e., co-occurrence of nevi with globular, reticular and complex patterns) were also more likely to develop a high-risk nevus phenotype.[18]

Across SONIC studies, we have shown that subsets of nevi that can be recognized by their dermoscopic patterns (e.g., reticular nevi and globular nevi) are biologically distinct. As previously noted, globular and reticular nevi differ in their associations with the patient's age and skin color, as well as in their predilection for different body sites.[6] Furthermore, we have shown in a convenience sample from adult patients that these subsets of nevi also differ in their genetic profile — globular nevi are associated with BRAF V600E mutation, which is also frequently observed in melanoma, whereas reticular nevi are mostly BRAF-mutation-negative.[19]

Relevance for melanoma diagnosis

Interestingly, in a pilot case-control study, we found that patients with melanoma more frequently harbored nevi with a complex (reticular-globular) pattern (**Figure 1D**), compared to patients without melanoma. We are currently expanding this study, to better characterize nevus phenotypes that herald a heightened melanoma risk.

Conclusions

We have gained important insights about the expected morphology and host associations of childhood nevi from SONIC and other studies. A comprehensive understanding of the rules by which nevi abide may help in the early detection of melanomas that break these rules. In addition, to inform melanoma prevention and screening efforts, we need to better stratify patients based on their melanoma risk. A thorough understanding of nevogenesis and of nevus phenotypes may improve our ability to predict patients' melanoma risk.

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Treatment of Pediatric Melanoma

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Melanoma in childhood has gained attention as the deadliest form of pediatric skin cancer. Childhood melanoma largely takes two distinct forms: the rare melanoma that arises in giant congenital nevi and the more common sporadic form. Most pediatricians now realize the importance of prompt evaluation and, when appropriate, excision of giant congenital nevi. But the sporadic form of childhood melanoma is roughly 10 times more common, and the use of tanning beds has undoubtedly contributed to the increasing incidence of this disease among young people.[1,2,3] This has prompted important legislative efforts aimed at curbing tanning bed use in the adolescent population. To date, 42 states and the District of Columbia have either restricted adolescent tanning bed usage or banned it entirely.[4]

Diagnostic Challenges

Increased awareness of the pediatric occurrence of a cancer previously thought to be almost exclusively entrenched in the adult population has led to greater scrutiny of children's pigmented lesions by parents and primary care practitioners alike. This has led to increased referral of children to dermatologists, generated greater numbers of skin lesion biopsies and revealed that a significant number of melanocytic neoplasms in children are diagnostically challenging, both clinically and histologically.

These neoplasms are known by a variety of terms, e.g., melanocytic tumors of uncertain malignant potential (MELTUMP) and atypical melanocytic proliferation (AMP).[5] Many bear a resemblance to the benign skin lesions first described by Sophie Spitz and are therefore termed atypical Spitz tumors (AST) or spitzoid tumors of undetermined malignant potential (STUMP). As pathologists seek to determine whether these histologically ambiguous lesions are benign or represent potentially deadly melanomas, they employ a variety of molecular tests aimed at better defining their risk. These include fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH) and, more recently, evaluation for *TERT* promoter mutations.[6] Despite these advances in molecular evaluation, a significant number of cases remain in diagnostic uncertainty after thorough workup. Proper management along the spectrum between benign lesion and melanoma poses great challenges for the physician, both in communicating the risk to an anxious family and in determining adequate but not overzealous treatment and follow-up.

The Keys to Proper Treatment

It is axiomatic throughout oncology (and throughout medicine in general) that proper treatment begins with a proper diagnosis; diagnostic uncertainty not only dramatically elevates patient and family concerns and anxiety levels but starts the therapeutic process off on the wrong foot. Along with the challenge of accurate diagnostic classification, pathologists also must accurately convey their assessments to the treating clinicians. Hence, optimal care of children with atypical or frankly malignant melanocytic neoplasms requires multidisciplinary efforts and accurate communication of test results and inferred risk, not only within the medical team but for patients and their families.

Continued on page 8

Continued from page 7

The Moffitt Five-Point Scale for Reporting Melanocytic Neoplasia

We have found that a five-point scale modeled in part on the five-point BI-RADS classification (Breast Imaging Reporting and Data System), developed by radiologists to convey risk of mammographic findings, can be an extremely useful tool for communication from pathologist to clinician, and in turn from clinician to the family and patient.[7] Our team adapted this alphanumeric system to integrate the findings of all available histologic, immunohistochemical and molecular test results and to communicate the histologic class and imputed risk of malignancy to clinicians and family (**Figure 1**).

First, the histologic class is assigned a letter describing its major feature. As most of these lesions resemble Spitz nevi, the most common prefix is S; others include B (blue nevus-like), C (congenital) and N (nevoid). Next, a number from 1 to 5 computing the assessed determination and expressing the degree of confidence in the benign or malignant nature of the lesion is assigned. Lesions determined to be unequivocally benign are assigned a score of 1, while clearly malignant lesions are scored a 5. Lesions with some features felt to be benign are assigned a 2, while those with serious abnormalities favored to be malignant are rated 4. Lesions are scored 3 when the balance of testing cannot determine their malignant potential.[8] Note that this classification schema does not specifically assign histologic findings to one category or another, and two pathologists might view the same lesion quite differently. The goal of the schema is not to achieve diagnostic consensus but to ensure accurate communication of the pathologist's assessment to the clinician.

For example, a lesion with the histology of an atypical Spitz tumor that demonstrates heterozygous loss of 9p21 on FISH would be described as an S4, as studies with limited follow-up have shown that these lesions have a propensity to metastasize to regional lymph nodes but rarely disseminate further. Patients in each diagnostic category receive

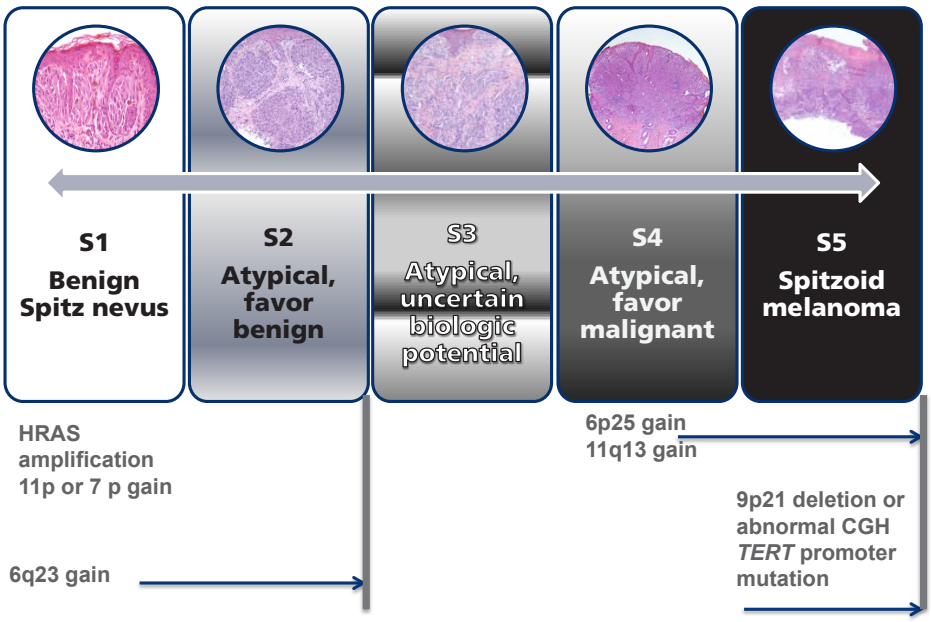

Figure 1. The spectrum of melanocytic neoplasia in spitzoid lesions on the Moffitt five-point scale, ranging from a benign Spitz nevus (category 1) through varying degrees of atypia (categories 2 through 4) all the way to spitzoid melanoma (category 5).

Genetic aberrations as assessed by fluorescence in situ hybridization and/or comparative genomic hybridization can be particularly helpful in classifying atypical lesions as either "favor benign" (category 2) or "favor malignant" (category 4), but even with all available histologic and ancillary information, some lesions remain difficult or impossible to categorize (category 3) as either "favor benign" or "favor malignant." The goal of the schema is to ensure accurate communication of the pathologist's assessment to the clinician. Courtesy of Jane Messina, MD; modified from Sreeraman Kumar R, Messina JL, Reed D, Navid F, Sondak VK. Pediatric melanoma and atypical melanocytic neoplasms. *Canc Treat Res* 2016; 167:331–369.

customized surgical treatment aimed at reducing risk of recurrence, regional nodal involvement and dissemination. At our institution, we treat S1 and S2 lesions with complete excision. We treat S3 and S4 lesions surgically to account for the "worst-case scenario," as if they were melanomas of comparable thickness. This includes wide excision and, when the lesion is ≥0.8 mm thick and/or ulcerated (T1b in the AJCC 8th edition staging system), sentinel lymph node biopsy; S5 is treated using standard guidelines for melanoma.[9]

Findings in the excision specimen or sentinel node can sometimes add to and modify the findings of the original biopsy and may result in reclassification of an S3 or S4 lesion to an unequivocally malignant S5. It is important to note that nearly all of our knowledge about "borderline lesions" and pediatric melanoma comes from retrospective reviews and registries.[5,10,11,12,13] Lesions considered to have been "atypical" in one series may later recur and be included in a different series as melanoma. While it is appropriate that each piece of clinical and pathological information be incorporated into diagnostic and therapeutic decision-making, having a clear record of what the lesion was thought to be at initial diagnosis and after definitive surgery (akin to the concepts of "clinical staging" and "pathological staging" embraced by the AJCC melanoma staging system) will go a long way to shed more light on the natural history of lesions recognized as atypical but not unequivocally malignant at initial diagnosis.

Surgical Management: Similar to Treatment in Adults

While the diagnostically challenging subset of pediatric melanocytic lesions garners much attention in the literature, the majority of melanocytic tumors removed in older adolescents are clinically and pathologically identical

to adult melanoma. In general, surgical management of pediatric melanoma is nearly the same as in adults, with the distinction that we rarely if ever employ excision margins greater than 1 cm for children 14 or younger.[9] Local recurrences of pediatric melanomas excised with a 1-cm margin have been essentially nonexistent in our experience. Sentinel lymph node biopsy is widely employed as a diagnostic and staging adjunct, but (as has recently become standard in adults) radical lymphadenectomy is often omitted for patients with positive sentinel lymph nodes. In contrast, clinically detected nodal involvement is routinely managed with radical lymphadenectomy, and we have now treated several pediatric patients successfully with neoadjuvant molecularly targeted therapy prior to lymphadenectomy, a strategy that is being employed increasingly in adults with BRAF-mutant clinical stage III melanoma.

Adjuvant Therapy

Adjuvant therapy for adult stage III melanoma has changed dramatically in the past five years. Interferon α-2b [Intron A®], once the only approved adjuvant option, has essentially been replaced by adjuvant use of immune checkpoint inhibitors (initially ipilimumab [Yervoy®] but now anti-PD1 antibodies, with nivolumab [Opdivo®] FDA-approved for this indication), as well as adjuvant use of combination dabrafenib [Tafinlar®] and trametinib [Mekinist®], a newly FDA-approved option for BRAF-mutant stage III melanoma. For pediatric patients, interferon α-2b, including the pegylated form, has proven better tolerated than in adults, and has been widely employed for children with sentinel node-positive or clinical stage III melanoma after surgery.[14]

Virtually no pediatric experience with adjuvant use of either ipilimumab or anti-PD1 antibodies has been reported. While adjuvant anti-PD1 monotherapy is generally quite well tolerated in adults, long-term endocrine and cardiac toxicities are recognized and would be potentially catastrophic developments in children.[15] Moreover, troublesome joint-related problems, likely various forms of autoimmune arthritis, have also emerged as late sequelae of immunotherapy treatment and could also disproportionately impact on a younger population.[16] Since BRAF mutations are common in pediatric melanoma, and since experience with BRAF and MEK inhibition in children has largely been favorable, we have recently considered combination dabrafenib-trametinib to be a more attractive option for adjuvant therapy of stage III pediatric melanoma when a BRAF mutation is present. BRAF mutation testing by immunohistochemistry and pyrosequencing or next-generation sequencing is now routinely conducted on all stage III melanoma cases at our institution.

Treating Stage IV Melanoma

Fortunately, stage IV melanoma is rare in pediatric patients. However, many cases of stage IV melanoma in young adults originated from primary tumors that arose before age 18;[11] hence, there is more "metastatic pediatric melanoma" than many oncologists realize. Despite the explosion of new treatment options for unresectable metastatic melanoma in adults (at last count, at least 11 drugs or combinations have received FDA approval for this indication since 2011), only one drug — ipilimumab — has received FDA approval for treatment of metastatic melanoma in children. Even this approval was not based on extensive experience in the pediatric population.[17]

Nevertheless, the drugs commonly used in adult stage IV melanoma represent the best option for those rare pediatric-aged patients with unresectable metastatic melanoma. Concerns over late toxicity in childhood melanoma survivors are a factor in unresectable metastatic melanoma, but in contrast to the adjuvant setting, these concerns take a back seat to the need for effective treatment of an immediately life-threatening condition. Hence, immunotherapy tends to be our first-line treatment option for stage IV melanoma in children just as in adults, using either single-agent anti-PD1 therapy (nivolumab or pembrolizumab [Keytruda®]) or combination ipilimumab plus nivolumab. As in adults, decision-making about single-agent versus combination immunotherapy involves complex calculations weighing the greater risk of toxicity against the higher response rate and progression-free survival with combination treatment. We generally prefer to use single-agent anti-PD1 therapy unless the disease is symptomatic, or when the tumor burden is very high even if asymptomatic, or when brain metastases are present in conjunction with extra-CNS disease.

"Many cases of stage IV melanoma in young adults originated from primary tumors that arose before age 18; hence, there is more 'metastatic pediatric melanoma' than many oncologists realize."

BRAF-mutant unresectable metastatic melanoma that is refractory to immunotherapy is treated with combination BRAF-MEK inhibition. There are now three FDA-approved combinations for adult use (dabrafenib+trametinib, vemurafenib [Zelboraf®]+cobimetinib [Cotellic®] and encorafenib [Braftovi™] +binimetinib [Mektovi®]), with little to indicate whether one combination would be better suited to pediatric use than another.

Cytotoxic chemotherapy has almost entirely been replaced as a treatment for metastatic melanoma by these various new drugs.

Conclusions

While the treatment strategies developed in adults have proven highly efficacious in most cases when adapted to pediatric patients, there is clearly a need for more prospective testing of therapeutic strategies in the pediatric population. Cooperative group, multicenter and even multinational studies will be required

Continued on page 10

Continued from page 9

for adequate testing, given the rarity of advanced melanoma in childhood. Moreover, centers with extensive experience in treating young adults should be encouraged to reassess their experience in those cases where the original melanoma was diagnosed in childhood. This will help in seeking further insights into optimal treatment approaches in both adjuvant and metastatic settings.

For the foreseeable future, we urge clinicians to refer all patients with pediatric melanoma or atypical melanocytic proliferations to clinical centers that have dedicated teams for the pathological evaluation and clinical management of these challenging but highly rewarding cases. We have found that excellent communication between family, pathologist, radiologist, surgical team, oncologist and referring physician is critical for the creation and implementation of the optimal plan. Educational efforts directed at pediatricians, family medicine providers and dermatologists would help further raise awareness of pediatric melanoma and the challenges faced by patients, families and providers when confronted with a suspicious pigmented lesion on a child's skin.

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From the Editors,
continued from page 1

Study of Nevi in Children, or SONIC, which has documented the morphology and evolution of thousands of nevi during childhood and adolescence. By helping to establish patterns followed by 'normal moles' in this age group, the SONIC data inform recognition of outlier lesions that deserve greater clinical consideration. In a companion piece, Drs. Carrera and Marghoob explore the contribution of dermoscopy (which has been embraced as an indispensable tool in clinical assessment of pigmented lesions) to the diagnosis of melanoma in childhood.

In our concluding article, Drs. Sondak, Messina and Reed present the "Moffitt Five-Point Scale for Reporting Melanocytic Neoplasia," which their group has developed to convey the risk of progression and metastasis associated with a given melanocytic lesion. They then explore how the revolutionary recent advances in targeted therapy (e.g., BRAF–MEK inhibition) and immunotherapy (e.g., checkpoint blockade) apply to the pediatric patient with advanced melanoma.

While melanoma incidence in childhood has risen, deaths remain few. Lowering this already low death rate while avoiding unnecessary biopsies, worry and morbidity will require further improvements in primary prevention, early diagnostic accuracy and therapy. We thank our authors for educating us about some of the most important advances in the field.

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