Series Editor: Camila K. Janniger, MD

Pediatric Malignant Melanoma: An Update on Epidemiology, Detection, and Prevention

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Since the mid–21st century, the incidence of melanoma has climbed faster than any other type of malignancy. To curb this trend, it is critical to identify children with factors that increase susceptibility to developing pediatric malignant melanoma (MM). Risk reduction is a complex process that involves detecting the rudiments of melanocytic tumors at the precancer stage, altering attitudes toward sunlight and suntans, and protecting the skin from UV damage.

Cutis. 2009;84:192-198.

Although malignant melanoma (MM) remains uncommon in children, the incidence of this deadly disease continues to rise in the general US population,[1,2] which means that the likelihood of American pediatric patients developing MM at some point in their lifespan is increasing. The rudiments of MM may be occurring in early childhood. Dermatologists serve in preventive care of melanoma by educating patients and caregivers, especially those with increased susceptibility, about modifiable risk factors. Intervention by early identification of suspicious lesions remains the key step in affecting melanoma cure. Sun protection education conducted at least annually is necessary to sustain sun protection practices throughout childhood. This article is a review of the clinical manifestations, risk factors, and prevention efforts against the development of pediatric MM.

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Epidemiology

The number of individuals diagnosed with melanoma nearly doubled every 10 years from 1930-1970; since then, the rate has declined, with the number of individuals doubling every 10 to 20 years.[1,2] The growing number of cases may be attributable in part to heightened awareness and changes in diagnostic criteria but likely also reflects a true increase in incidence.

This once rare cancer is now predicted to develop in 1 in 82 women and 1 in 58 men in the United States.[2] The American Academy of Dermatology estimates that 121,840 new cases of melanoma will be diagnosed in 2009, of which 68,720 will be invasive.[3]

Although only 2% of cases of MM occur in individuals 20 years or younger, with 0.3% to 0.4% of all cases (including rare congenital cases) presenting before puberty, this age group also is experiencing an increase in absolute case numbers.[1,2] Current data estimate that among children aged 0 to 9 years, MM arises in 0.7 per million per year. This incidence rate increases to 13.2 per million per year in individuals aged 15 to 19 years. In individuals aged 20 to 35 years, MM becomes a leading cause of cancer and cancer-related deaths, which confirms that prevention is vital to avert carcinogenesis in childhood and adolescence.[1,2,4]

Epidemiologic factors differ somewhat in children compared to adults. An analysis of 3158 patients with melanoma (age range, 1–19 years) in the National Cancer Data Base found that cutaneous melanoma occurred in a higher proportion of female and nonwhite patients when compared with adults, though white patients still accounted for most cases. In an interesting turn, disease thickness in the younger age group did not necessarily correlate with survival.[4] The incidence

of MM, especially invasive cases, in patients with skin of color appears to be rising, particularly among the large and predominantly young Hispanic and Latino populations in California.[5]

Diagnosis

In 1985, the ABCD algorithm was introduced as an easily remembered mnemonic to aid in early recognition of MM.[6] Suspicious lesions exhibit some combination of asymmetry, border irregularity (ie, spicule formation, notching), color variegation (ie, more than one color; alterations in color; black lesions; lesions that are red, white, or blue), and/or diameter greater than 6 mm (acquired lesions should be smaller than the size of a pencil eraser). Recently, *E* for evolving or evolution (ie, any change in size, shape, symptoms, surface, or color; new lumps or bumps in a lesion or sites of bleeding or discomfort) has been added to enhance the algorithm's specificity and sensitivity. This latter criterion has been reconfirmed as an important screening feature.[7] While not all melanomas exhibit all features of the ABCDE algorithm, enhanced diagnostic accuracy results when a lesion fulfills more than one criterion. The features of a melanoma can be delineated further when patients are examined in the context of their own predominant clinical and dermoscopic nevus patterns. The ugly duckling among nevi, both in clinical appearance and dermoscopic pattern, often signals abnormal melanocytic proliferation.[8]

Diagnosing MM in children can be challenging for even the most experienced physician. Misdiagnosis in children has been reported in as many as 40% of cases,[9] and it is associated with morbidities including delayed therapy, unnecessary procedures, and patient and caregiver anxiety. Misdiagnosis often is rooted in the lack of vigilant surveillance of younger populations, the atypical clinical appearance of pediatric melanoma, and the clinical mimicry of benign neoplasms. A subset of nodular melanomas of childhood present as pyogenic granuloma–like lesions.[10] In childhood, many benign lesions exhibit melanomalike features. A retrospective study evaluated 33 pediatric patients with cutaneous melanoma. The authors compared the pediatric patients to adults and determined that childhood melanoma presented more frequently as a nodular, pedunculated, or amelanotic lesion,[11] all of which are more difficult to diagnose. Prognostically, survival rates of 21% to 79% at 5 years have been reported, with 0% survival from metastatic MM arising in a giant congenital melanocytic nevus (GCMN).[12]

Dermoscopy has emerged as a useful tool that allows physicians to clinically monitor congenital melanocytic nevi (CMN) as opposed to prophylactic excision of such lesions. Dermoscopic features of CMN usually present in homogeneous patterns and include reticular or honeycomblike networks; sharply circumscribed, round to oval aggregates of brown-black pigment; diffuse brown background pigmentation; milialike cysts; hypertrichosis (often a late feature); and perifollicular pigmentation.[13] If a change from prior dermoscopic examination or a large deviation from the patient's dermoscopic patterning (the dermoscopic ugly duckling) is noted on follow-up, the pigmented lesion should be excised and analyzed by a pathologist. The physician also should perform a biopsy on any lesion that exhibits characteristic melanoma features, such as irregular, prominent, and broad pigment network; black dots; radial streaming; irregular brown globules; gray-blue areas; and white scarlike areas.[13] Reevaluation of questionable lesions after 3 months provides adequate time to detect evolution.

Even in childhood, regular dermatologic evaluation is needed for patients with dysplastic nevi (Figure 1), GCMN, more than 50 nevi, syndromes predisposed to cutaneous malignancies (eg, xeroderma pigmentosum [XP]), or a family history of melanoma syndromes. Early diagnosis and repetitive continued evaluation is vital in families with genetic causes of MM. Patients with suspicious nevi or a family history of melanoma require at the least an annual examination, both dermatologic and ophthalmologic (for familial cases). Mole mapping through photography can be performed to aid in long-term reevaluation and, based on our experience, is particularly helpful in patients with more than 50 nevi.

Pediatric patients and their caregivers can be taught to look for signs of melanoma between dermatologic examinations. Patients should be educated using the ABCDE algorithm for monthly self-examination and should ask themselves the

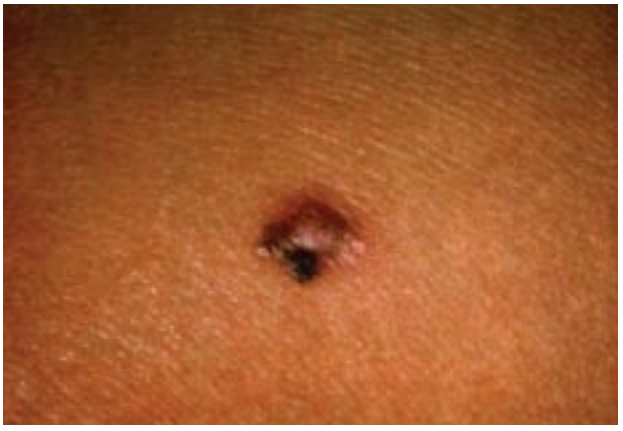

Figure 1. Dysplastic nevus measuring 1.2 cm excised from the thigh of an 8-year-old Asian girl.

following questions when performing monthly self-examinations or examination of their children for moles: Is one half different from the other? Are the edges ragged or blurred? Are there multiple colors? Is the lesion larger than a pencil eraser? Has the mole increased in size or changed in any way? Answering yes to any of these questions warrants an immediate appointment with a dermatologist or pediatric dermatologist. Patients also should be counseled to seek clinical assessment for any symptoms associated with a pigmented lesion, such as bleeding, pruritus, or regional lymph node enlargement.

In a small series of children with melanoma, most presented due to increasing lesion diameter with rare complaints of asymmetry, border irregularity, or color change.[10] As a rule of thumb, most CMN grow only 2 to 3 times their original size from birth to adulthood. Lesions that double or triple in size within a few months are considered to be growing abnormally, warranting excisional biopsy. Suspicious lesions should be excised and appropriate pathologic examination performed (Figure 2).

Risk Factors

The risk factors for MM can be categorized as heritable or unmodifiable factors, such as skin color or eye color, or preventable factors, such as cumulative sun exposure (Table). One clinical lesion previously believed to warrant excision is the halo nevus. However, it has been demonstrated that excising typical-appearing halo nevi is unnecessary because these lesions generally are benign.[14] One should consider that new-onset generalized vitiligo occasionally has been found as a response to melanoma and screening of new cases for changing or atypical melanocytic lesions is recommended.[15]

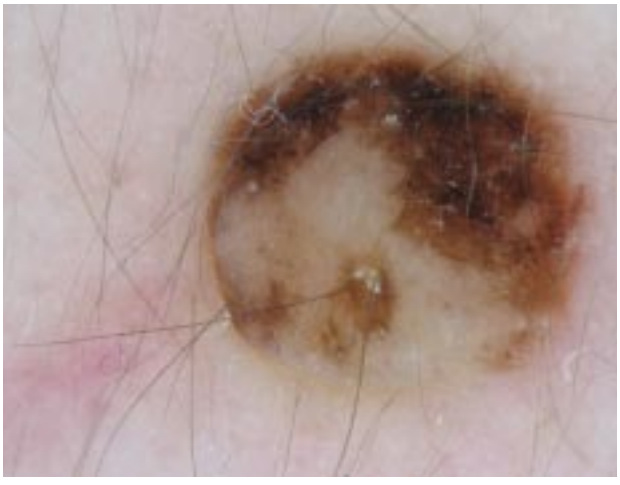

Figure 2. Irregular 1.5-cm^2 nevus on the back of a 16-year-old adolescent girl. Excisional biopsy showed mild dysplastic features.

Acquired Nevi—Exaggerated nevus counts also are known to be strong predictors of the risk for developing MM.[16] Furthermore, multiple nevi often can be prevented. In a prospective randomized study of 309 white school-aged children, the group receiving sunscreen for 3 years and proper application instructions developed fewer new nevi, particularly on the trunk and upper and lower limbs, compared with controls.[17]

It is unknown if neonatal phototherapy, the treatment of choice for hyperbilirubinemia, increases the risk for developing melanoma. It has been reported that neonates who undergo intensive phototherapy develop more nevi, sometimes atypical nevi, than children with no such medical history.[18] Although higher numbers of nevi acquired from sunlight are linked to an increased risk for melanoma, it is unknown if nevi from phototherapy pose a similar risk. A retrospective case-control study found no significant risk for developing melanoma during childhood after neonatal phototherapy (P=.08).[19] However, median follow-up time was only 18 years, thus there was no exploration of an association with adult-onset disease. Photoprotection should be recommended to all patients who receive phototherapy until its impact on future MM risk is investigated more fully.

Congenital Melanocytic Nevi—Congenital melanocytic nevi are divided into 3 groups based on size: small, medium, and GCMN. These lesions occur in 1 in 20,000 neonates[20] and are defined as GCMN when measuring 20 cm^2 in an adult or covering a full body region. Melanoma has been reported in 4% to 6% of cases and can be cutaneous or intracranial, the latter being universally fatal.[12,21] While focal changes within these lesions may be cause for concern, congenital irregularities such as erosions or ulcerations in GCMN may be common and benign in nature.[22] Prophylactic excision has been advocated when possible, both to reduce melanoma risk because the lesions can be difficult to monitor, especially on the scalp, and for cosmetic benefit to the patient; however, this procedure is curtailed when neurologic symptoms of leptomeningeal disease are present. Excision of the cutaneous aspect of GCMN does not eliminate the risk for intracranial melanoma associated with GCMN. Neurocutaneous melanosis is more common with GCMN in an axial location and when more than 20 satellite lesions are noted.[23] Magnetic resonance imaging or a computed tomographic scan is required when intracranial disease is suspected. The highest risk for malignant transformation of a GCMN has been reported to occur before 10 years of age.[24,25]

Risk Factors for the Development of Pediatric Malignant Melanoma

Heritable or Unmodifiable Risk Factors
Blond or red hair (natural)
Blue or green eye color
Burns easily, tans rarely
Family history of melanoma (cutaneous or ocular)
History of dysplastic nevi
High nevus count (in FAMMM) or family history of melanoma and/or pancreatic cancer
Living close to the equator
Xeroderma pigmentosum
History of immunosuppression associated with solid organ transplantation or chemotherapy

Preventable Risk Factors[a]
Ephelides
Excessive sun exposure and/or blistering sunburn before 18 years of age
High nevus count
GCMN/neurocutaneous melanosis
Medications
Photosensitizing agents
Immunosuppressive agents
Exposure to indoor tanning equipment (≥1 occasion)

Abbreviations: FAMMM, familial atypical multiple mole melanoma syndrome; GCMN, giant congenital melanocytic nevus.
[a]Prevention is achieved through photoprotection and avoidance of exacerbating factors.

It is debated if small and medium CMN should be prophylactically removed because the incidence of malignant conversion is uncommon, though many melanomas after puberty do arise in a pigmented lesion such as a CMN or acquired melanocytic nevus. While rare, congenital melanoma that develops in utero or via transplacental metastases does occur and should be considered when assessing congenital pigmented lesions.[12] As the risk is considered low, most patients, physicians, and caregivers opt for long-term observation of nevus configuration rather than blanket excision. Excision can be performed for physically disfiguring or atypical CMN. Physicians and patients must be aware that while removing melanocytic cells reduces the risk for malignant transformation, excision of the CMN does not guarantee protection against melanoma. A systematic review of 18 studies with 6571 patients demonstrated 49 MM in 46 patients (0.7%). Of the MM, the authors found that 33 of 49 (67%) melanomas occurred within the CMN, 5 (10%) occurred in the skin outside of a CMN, 4 (8%) developed at an extracutaneous primary site, and 7 (14%) had no identifiable, primary tumor.[25] Primary cutaneous melanomas (5 tumors in 3 patients) originated outside the CMN in one study, with one incidence of melanoma formation beneath a previously excised lesion.[26] This finding highlights the fact that complete excision of CMN requires excision down into the fat to eliminate the complete hair follicle, which often is involved in CMN. Occasional malignant conversion of other types of CMN, such as the nevus spilus,[27] which consists of a café au lait macule speckled with small melanocytic nevi, or a Becker nevus (smooth muscle hamartoma),[28] have appeared in the literature. All CMN should be monitored sequentially over time for alterations. Observation spans can range from every 6 months in at-risk patients to every 2 years in low-risk individuals.

Cumulative Sun Exposure—In most individuals, MM risk strongly correlates with cumulative UV exposure, thus primary care physicians, pediatricians, pediatric dermatologists, and dermatologists serve in primary prevention by educating children and caregivers on the importance of limiting time in the sun and the proper application of sunscreen. Children with light hair and eye color need to exercise extra vigilance. In our experience, many individuals erroneously believe that indoor tanning equipment is safe and, in fact, can prevent sun damage. It has been reported that as many as 47% of adolescent girls or young adults aged 17 to 18 years have used indoor tanning equipment at least 3 times.[29] This practice is more likely among adolescents with caregivers who also frequent a tanning salon; therefore, both teenaged patients and their caregivers need to be cautioned about the risks for UV light from indoor tanning equipment. Epidemiologic data have shown that use of indoor tanning equipment even once in one's lifetime increases the risk for developing melanoma; furthermore, individuals exposed in their youth exhibit greater vulnerability to the carcinogenic effects of indoor tanning equipment.[29-32] Thus,

childhood and adolescent use must be avoided without exception.

Immunosuppression—Immunosuppression is another risk factor for melanoma formation. Cutaneous carcinoma has been reported to be the most common malignancy following pediatric renal transplantation[33] and the second most common among all pediatric transplant recipients.[34] In one retrospective study of more than 10,000 organ transplant recipients, of all pediatric allograft recipients diagnosed with skin cancer, only 16% developed the disease during childhood with an average delay in tumor onset of more than 10 years posttransplant. Melanoma accounted for a higher percentage of skin cancers within pediatric transplant recipients compared with adult recipients (12% vs 5% of cutaneous malignancies).[34] Pediatric patients with genetic immunodeficiency syndromes, prior malignancies, and exposure to chemotherapy also are at risk. One reason for this increase in melanoma may be that immunosuppressed children, irrespective of race and ethnicity, have been shown to have more nevi than age-matched controls,[35] an independent risk factor for melanoma.

A current issue for dermatologists remains if cutaneous immunosuppressive agents, such as calcineurin inhibitors, will promote cutaneous photocarcinogenesis. In March 2005, the US Food and Drug Administration issued a public health advisory about a potential cancer risk from use of topical pimecrolimus and tacrolimus based on animal studies and case reports in a small number of patients.[36] However, a randomized controlled trial found no increased incidence of nonmelanoma skin cancer after 4 years in 9800 patients treated with topical tacrolimus for an average of 7 months.[36,37] A longer period of observation and further study are required to resolve this issue. In the meantime, children and adolescents treated with topical immunosuppressive agents must be targeted for skin cancer prevention and surveillance.

Genetics of MM—Roughly 5% to 10% of patients with MM have a family history of melanoma. Some of these cancer-prone families also develop multiple dysplastic nevi, an association referred to as familial atypical multiple melanoma or atypical nevus syndrome. The first report of familial melanoma dates back to the early 19th century,[38] but genetic susceptibility has only been examined in the last few decades. Germline mutations in the cyclin-dependent kinase inhibitor 2A (9p21) gene, *CDKN2A*, have been linked to an inherited predisposition to multiple MM (>3) with or without familial pancreatic cancers or MM.[39] However, it has been suggested that the gene, which encodes $p16^{Ink4a}$ and $p14^{Arf}$, is only rarely associated with childhood and adolescent disease.[38-40] Mutations of the cyclin-dependent kinase 4 (12q14) gene, *CDK4*, also have been shown to confer an increased risk for cutaneous MM but do not account for early-onset disease.[40] Average age of *CDK4* mutation–associated MM onset is 46 years.[41] A third high-penetrance, unidentified susceptibility gene has been localized to 1p22 and linkage evidence was shown to be strongest in families with the earliest age at diagnosis.[42]

Numerous syndromes confer a genetic susceptibility to MM including XP, a rare spectrum of illnesses with defective DNA repair. Seven clinically distinct forms of XP plus one variant have been described, each inherited in an autosomal recessive fashion. In 75% of children, XP manifests by kindergarten with easy sunburning; acute photosensitivity; freckling; xerosis in sun-exposed areas; and eventually with keratitis, premature elastosis, and wrinkling. The first skin cancers are detected by a mean age of 8 years. Currently, treatment is limited to early preventive care, including sunscreens, sun protective clothing, UV-blocking window shields to prevent indoor exposure, and avoidance of daytime outdoor activities; thus, early recognition is crucial. In an in vivo study with UVB-irradiated XP mice, subcutaneous injection of recombinant adenovirus carrying the human XP complementation group A gene, *XPA*, led to expression of the XPA protein in basal keratinocytes and prevention of adverse effects such as late development of squamous cell carcinoma.[43] These results add promising support to the existing research efforts aimed at establishing gene therapy as the treatment of XP.

Other syndromes linked to a substantial risk for melanoma include hereditary retinoblastoma,[44] Werner syndrome,[45] melanoma-pancreatic carcinoma syndrome,[46] and breast cancer syndromes including Li-Fraumeni.[47]

Risk Modification of MM Acquisition and Early Detection

"Malignant melanoma is, gram for gram, arguably the most malignant neoplasm in man."[48] Therefore, prevention and early diagnosis are vital. Malignant melanoma prevention is an evolving concept. As it is unclear when educational intervention is most effective for patients using sunscreen and practicing sun avoidance, repetitive review of the topic is required. Education of young adolescents in sun protection is more effective when multiple sessions of education occur.[49] A survey exploring sun protection behaviors of the offspring of women with skin cancer revealed that when the mother's diagnosis occurred more than 2 years prior, the children were less likely to use

sunscreen, more likely to use indoor tanning equipment, and more likely to sustain a sunburn compared to children whose mother had been diagnosed more recently.[50] These results further emphasize the necessity of repeated intervention.

Both children and caregivers should be taught basic sun protection, which involves avoiding midday sun (10 AM–4 PM); wearing sun protective clothing; and using extra caution around water, sand, and snow. The American Academy of Dermatology recommends liberally applying sunscreen to all exposed areas with a minimum sun protection factor (SPF) of 15 at least 15 to 30 minutes prior to going outdoors, with reapplication every 2 hours and after swimming or sweating.[51] An egg-sized amount of sunscreen should be used each time. Patients often do not apply sunscreen adequately, thus higher SPF may be needed to counteract inadequate application techniques. Sunscreens are not permanent; they wash and sweat off after an hour of swimming or sweating. Reapplication is important to maintain the full SPF of any product. Complete avoidance of indoor tanning equipment is vital for long-term MM prevention.

Adequate sunscreens provide protection against both UVA and UVB light. Patients should be told that SPF only reflects protection against UVB light and taught to read labels for specific ingredients, such as avobenzone, titanium dioxide, or zinc oxide, which impart UVA protection. Unfortunately, avobenzone may breakdown with UV light exposure. Newer sunscreens composed of filters that contain a stabilizing ingredient for avobenzone recently have been approved by the US Food and Drug Administration (eg, butyloctyl salicylate and ecamsule).[51] Novel sunscreens that are colorful and child friendly may be used. Use of combination products with sunscreen and insect repellant is discouraged because reapplication may result in toxic exposure to diethyltoluamide, the active ingredient in most insect repellants.

Conclusion

Although the incidence of pediatric MM compared to adult melanoma continues to comprise a small fraction of total disease, it has become clear that childhood and adolescence are critical times for establishing and practicing effective sun protective behavior and modifying future risk.

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