Update on Malignant Melanoma in Children

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Malignant melanoma is a rare event in children. Yet, the overall incidence has consistently risen in the past 20 years. Thus, the likelihood that our pediatric patients will develop malignant melanoma is increasing. Previously, the bulk of lesions were estimated to occur in children with large congenital melanocytic nevi. Recent reports, however, have highlighted new risk factors for malignant melanoma in children, while demystifying other entities previously believed to have a grave prognosis. Knowledge of risk factors and participation in public health efforts toward prevention and early intervention can help the practitioner protect pediatric patients from this malignancy.

The lifetime incidence of melanoma in 2000 was estimated at 1 in 71 Americans. This number has risen steadily since 1930, when the risk was 1 in 1500 individuals. This suggests that, of the children seen in our practices, at least 1 in 71 will ultimately develop malignant melanoma. Melanoma is a leading cause of cancer in women between the ages of 25 and 44 years, confirming that prevention is vital to avert the carcinogenesis in childhood and adolescence. Melanoma in individuals 20 years or younger only accounts for 2% of disease, with prepubertal illness representing 0.3% to 0.4% of all cases. The most recent large case series of melanoma in children consisted of 13 patients. Sixty-two percent of these lesions arose in melanocytic nevi, highlighting the importance of mole examination and mapping in children. A 66.7% rate of mortality was seen because of melanoma-related causes. The 10 patients with primary cutaneous disease only had a 40% rate of 5-year survival. Thus, although the incidence of melanoma is low in children, survival rates may be quite poor. Early detection represents the best means of improving survival; the 5 patients with nonmetastatic lesions had a 100% 5-year survival.[1] Melanomas tend to occur on the limbs in females and the torso in males; this is likely due to the preferential occurrence of nevi in these locations in early childhood.[2]

The most important modifiable risk factors relate to ultraviolet (UV) light avoidance. UVB light has been shown to alter DNA structure through the formation of pyrimidine dimers. Cumulative damage of melanocyte DNA over time can result in melanoma formation.

It behooves us to identify children with unmodifiable risk factors as quickly as possible, protect them from UV damage, and detect carcinogenesis as rapidly as possible. Skin cancer prevention should begin with instruction in the nursery and continue through adolescence, when it is particularly important for us to educate our patients on the risks of tanning and sunbathing. Physical characteristics such as light hair and eye color should signal the need for early intervention.

One risk factor for melanoma formation is immunosuppression. Immunosuppressed children have been shown to have more nevi than age-matched controls.[3] This occurs irrespective of race and ethnicity. In addition, exaggerated nevus counts have been linked to greater melanoma risk. Although this has been linked primarily to nonmelanomatous skin cancers, melanomas also have been shown to be more common in long-term studies of patients who had undergone organ transplantation. Furthermore, following treatment of childhood cancer, melanoma is one of the common "second" malignancies seen.[4] It is unclear whether this is because of poor immune surveillance or is an extension of the larger nevus counts seen in these children.

The major culprit in melanoma formation in children and adolescents is the cumulative damage of UV light. Both UVA and UVB lights penetrate the ozone layer. When phototherapy is administered, the exaggerated UV dosing may increase cutaneous carcinogenesis. Psoriasis patients treated with PUVA (psoralen plus UVA) have an increased lifetime risk of melanomas.[5] As a result, phototherapy is used only sparingly in children. Furthermore, ocular

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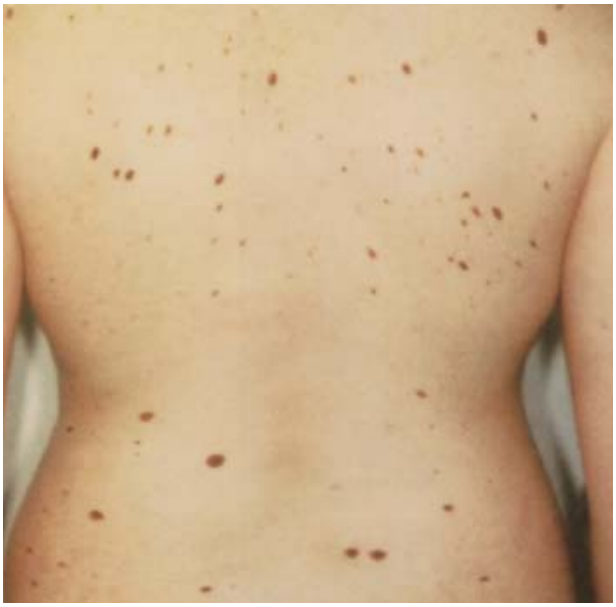

Figure 1. A 20-year-old male with hundreds of dysplastic nevi and a family history of melanoma. (Photograph courtesy of Anthony J. Mancini, MD.)

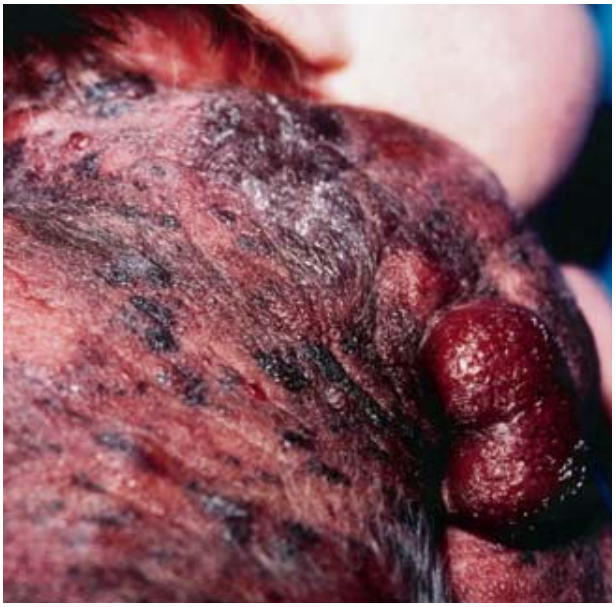

Figure 2. Ulcerations and nodules in a large congenital melanocytic nevus.

melanomas must be vigorously avoided in children on systemic psoralens through consistent usage of protective eye gear. Teenagers also must be warned against the use of unregulated UV light administration in tanning salons. Tanning booths may provide unregulated amounts of UVA light. Generally, users match or exceed maximum recommended doses and are not monitored by salon attendants.

The most recent question for dermatologists remains whether cutaneous immunosuppressive agents, such as tacrolimus and ascomycin, will promote cutaneous photocarcinogenesis. Initial studies in laboratory animals have suggested that photocarcinogenesis is unlikely to occur; however, only time will tell in humans. Until further studies are performed, photoprotection should be recommended in all patients using cutaneous immunosuppressive agents.

One clinical lesion that was previously believed to warrant excision is the halo nevus. In fact, a recent article has demonstrated that because of their low malignant potential, typical-appearing halo nevi are generally benign and do not warrant excision.[6]

Familial melanoma syndromes have been reported for many years. Recently, mutations have been detected that help explain the pathogenesis of these syndromes. The CDKN2A germ-line mutation results in a mutant p16 protein, which is unable to bind cyclin-dependent kinases. These mutations have been associated with dysplastic nevi formation (Figure 1), as well as early-onset, familial, and multiple cutaneous melanomas. In addition, children of mothers with breast or ovarian cancer have an increased incidence of malignant melanomas, thus history of any familial carcinomas should be thoroughly investigated.[7,8]

Numerous syndromes with cutaneous carcinogenesis have been reported. The most striking is xeroderma pigmentosum (XP), a spectrum of illnesses with defective DNA repair. XP subtypes A through G and a variant subtype have been described. Seventy-five percent of children with XP will manifest by kindergarten with easy sunburning, acute photosensitivity, freckling, xerosis in sun-exposed areas, and eventually, with keratitis and premature elastosis and wrinkling. The first skin cancers are detected at a mean age of 8 years. Numerous genetic loci have been found. Linkage of the D subtype of XP with the PIBIDS (photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, short stature) and the B subtype of XP with the Cockayne syndrome has been recently demonstrated. These latter 2 disorders are part of a group of premature aging syndromes due to helicase repair defects, but they lack the proven melanoma predisposition of other XP patients. Early recognition and early institution of photoprotection—including UV-blocking window shields and avoidance of daytime outdoor activities—are vital. Currently, gene therapy is being investigated for the treatment of XP.[9]

Congenital melanocytic nevi have been divided into small, medium, and large (or giant). The latter is defined by an expected adult size of greater than 20 cm in diameter or involvement of a complete region (eg, bathing trunk nevus). Large congenital

melanocytic nevi (LCMN) occur in 1 in 1000 to 1 in 20,000 neonates. These nevi may have neural differentiation, nodule formation, and satellite lesions. Neurocutaneous melanosis and leptomeningeal melanoma may be associated with and can lead to mental retardation, seizures, and early death. Traditionally, LCMN convert to melanoma in 4.5% to 10% of patients.[10] This risk reflects a combination of melanoma formation intracranially and cutaneously. In a group of 289 patients recently described in an LCMN clinic and through literature review, axial location was found to confer the highest risk.[11] Melanomas also may be congenital in these patients. Furthermore, it has been shown that satellite lesions, which may be numerous, are far less likely to undergo malignant conversion. Nodule and ulcer formations have been considered markers of malignant conversion. However, a recent report highlights that this may be a common process in LCMN (Figure 2).[12] Wu et al[1] reported the largest melanoma case series in children with a total of 13 tumors. The average age of the patients was 9 years, with 54% being male. Three of the lesions (23%) were detected in LCMN. All 3 of these melanomas were metastatic and were detected at an average age of 3.7 years; 2 melanomas were intracranial.[1] However, given the difficulty in assessing malignant transformation in lesions, which are often irregular in pigmentation and texture, biopsy is still warranted in newly formed nodules. Treatment involves tissue expansion, serial excisions, and grafting, when needed. Although mole removal reduces the risk of melanoma, intracranial disease cannot be eliminated. Magnetic resonance imaging of the brain is recommended for axial lesions and for children presenting with neurologic signs.[13] Surgery is not performed until it is determined that a child does not have symptomatic leptomeningeal disease.

Prevention of malignant melanoma requires a multidimensional approach. Use of sunscreen alone has been linked to increased nevus formation,[14] and controversy exists as to whether sunscreens are effective in melanoma prevention. Although we may recognize susceptible patients, educating them about sun protection is often arduous and unrewarding. However, educational public health efforts in Australia have been successful at stemming the growing incidence of melanomas.

Comment

The first step in the care of patients with suspicious nevi or a significant family history is annual examination and mole mapping through photography. Excision of suspicious lesions should be performed with appropriate pathologic examination. The ABCDEs of melanoma should be taught to patients and parents. At the onset of puberty, young women should be taught to perform self-skin and self-breast examinations on the third day of the menstrual cycle. Similarly, adolescent males should be taught to do self-skin examination with monthly testicular self-examination. These efforts should be combined with basic sun protection, which involves the avoidance of the midday sun from 10 AM to 3 PM, use of sun-protective clothing, and liberal application of sunscreen. Adequate sunscreens should provide protection against UVA and UVB light. Sunscreens with a sun protective factor (SPF) of greater than 30 should be used.[15] Patients should be told that the SPF only reflects protection against UVB light; also, patients should be taught to read labels for specific ingredients, such as avobenzone, titanium dioxide, or zinc oxide, which impart UVA protection. Application of an egg-sized amount of sunscreen and frequent reapplications should be explained. Novel sunscreens

Unmodifiable and Modifiable Risk Factors

Unmodifiable Risk Factors

- Blond or red hair (natural)
- Blue or green eye color
- Burns easily, tans rarely
- Family history of melanoma
- Previous history of dysplastic nevi
- Many moles: <20-year-old patients with ≥50 moles or >20-year-old patients with ≥100 moles
- Familial melanoma syndromes
- Living close to the equator
- Xeroderma pigmentosum
- Leptomeningeal melanocytosis

Modifiable Risk Factors

- Ephelides
- Vitiligo
- History of excessive sun exposure and/or blistering sunburn before the age of 18 years
- Many moles: <20-year-old patients with ≥50 moles or >20-year-old patients with ≥100 moles
- Large congenital melanocytic nevi
- Medications
- Photosensitizing agents
- Immunosuppressive agents

that are colorful and child-friendly may be used. Combinations of sunscreen and insect repellant are not encouraged, because reapplication may result in toxic exposure to diethyltoluamide (DEET), the active ingredient in most repellants. In addition, sun-protective clothing should be encouraged. Patients are rarely aware that the average white T-shirt only has an SPF of 8. Recently, a rinse has become available that can be used in the washing machine to increase the SPF of clothing and is needed only every 20 washes. The full combination of sun-protective activities and clinical care is required to ensure adequate care of the pediatric patient with nevi.

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