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Pediatric melanoma

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ABSTRACT

Childhood melanoma is a rare pediatric malignancy, with fewer than 500 new diagnoses annually. The incidence is increasing, particularly in the adolescent population. This review highlights the epidemiology, clinical presentation, and histopathologic challenges of pediatric melanoma. Surgical resection remains the cornerstone for localized and regionally advanced disease. Adjuvant therapies, including current options and potential novel therapeutics for this unique population will be discussed.

Introduction

Although melanoma is one of the most common malignancies affecting adults, it is relatively a rare disease in children. Melanoma ranks fifth among all cancers in adult males and seventh in adult females, and it is the most common cancer among women 20–29 years of age.[1–3] Despite also being the most common skin cancer in children and adolescents, melanoma is still rare in children, with only 300–500 new pediatric diagnoses annually.[2,4,5] While the care of adults with melanoma is guided by evidence from multicenter clinical trials, the care of children with melanoma is limited by the lack of clinical trials specific to the pediatric population.

Pediatric melanoma is known to have clinical, epidemiological, and pathological characteristics that are distinct from adult melanoma. Although pediatric melanoma may arise from healthy skin or a pre-existing nevus, it may also arise from transplacental transmission or in the setting of predisposing conditions including xeroderma pigmentosum or giant congenital melanocytic nevus.[2,4,5] Children with melanoma more often present with thicker lesions, regional nodal involvement, and distant metastases when compared to adults, but survival for children is better than adults with melanoma of similar stage.[4,6–9] Despite these differences, current treatment strategies for pediatric melanoma have largely been adapted from adult guidelines based on trials that rarely include pediatric patients.

Epidemiology

Over the past 3 decades, the incidence of melanoma has increased markedly among both the adult and pediatric populations, yet still only accounts for 2% of all skin cancer diagnoses in the United States. Melanoma is the most common skin cancer among those less than 20 years of age, and currently accounts for 8% of cancers in adolescents.[2,10,11] Multiple studies have found that the incidence of melanoma in adolescents is rising as quickly as 3% per year.[2,7] Younger children with melanoma are more likely to be non-Caucasian and have head and neck tumors, while adolescents with melanoma are more likely to be female and present with trunk and lower extremity lesions.[10]

Pediatric melanoma, particularly in younger, prepubertal children, is thought to be a biologically unique disease entity that manifests different clinical characteristics. Compared to adults, many children present with higher rates of lymph node metastasis, thicker lesions, and more advanced stage of disease.[2,7,12,13] Despite these differences, the outcomes of children with melanoma are encouraging, with 70–80% overall survival rate at 10 years for all stages combined.[2,14]

Clinical presentation

Pediatric melanoma encompasses a rather heterogenous group of patients, including neonates, children, and adolescents, with a variety of distinct clinical presentations. While pediatric melanoma can develop de novo from previously healthy skin or from a dysplastic nevus, it can also arise in the setting of a genetic predisposition syndrome, a large congenital melanocytic nevus (CMN), or result from transplacental transmission.

Development from healthy skin

Almost half of all childhood melanomas arise de novo from previously healthy skin. The classic ABCDE characteristics (asymmetry, irregular border, more than one or uneven distribution of

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color, diameter >6 mm, and evolving or changing nevus) should raise concern for melanoma.[14,15] However, childhood melanomas may frequently be amelanotic, so any suspicious lesion, even if lacking classic characteristics, merits further evaluation. A modified criteria for suspicious lesions in children (amelanotic, bump/bleeding, colorless/uniform color, de novo/any diameter, and evolution or changing) has been proposed, but not yet validated.[14]

Clinical evaluation includes a complete skin evaluation with documentation of any pigmented lesions, including mucosal surfaces and interdigital spaces. Regional nodal basins adjacent to any suspicious lesion should be carefully evaluated given the higher incidence of lymph node involvement in pediatric melanoma. Suspicious lesions should be biopsied in a full-thickness manner to preserve information about the depth of the lesion.[3,5,14]

Development from a precursor lesion

Melanoma in children is much more likely to arise from a precursor lesion than in adults. Nearly one-third of childhood melanomas arise within a congenital melanocytic nevus or from a dysplastic or changing nevus. In adolescents, risk factors for the development of melanoma within a nevus mirror those of adult melanoma, including atypical or multiple nevi, ultraviolet (UV) radiation exposure, and fair skin.[14] Since prepubertal children who develop sporadic melanoma are more likely than adolescents to be non-Caucasian and without significant UV exposure, its role in this subgroup remains uncertain.

Approximately 1–3% of neonates are born with congenital melanocytic nevi, pigmented lesions containing actively proliferating melanocytic cells.[10] These lesions are classified by size and may achieve sizes >60 cm. The risk of malignant transformation of smaller lesions remains low (1–5%) with most diagnoses of melanoma arising from these lesions made in adulthood, while the risk for giant lesions is much greater (5–20%), with 1% of patients developing melanoma by 15 years of age.[10,14,16] Due to the risk of malignant transformation, larger lesions are surgically excised whenever possible. However, prophylactic excision does not completely eliminate the risk of melanoma, and all lesions, whether removed or not, should be followed closely by an experienced clinician.[5,10] Children with three or more small to medium lesions or a single giant congenital melanocytic lesion are at risk for neurocutaneous melanoma.[14] While extremely rare, unexplained neurologic symptoms including headache, vomiting, seizure, and motor disturbance should prompt further evaluation and imaging.[14,16,17]

Transplacental transmission

Melanoma is one of a unique group of malignant tumors that can be transmitted across the placenta during pregnancy. Since melanoma is one of the more common malignancies of young women, it accounts for 8% of all malignancies diagnosed during pregnancy and is the most frequent malignancy to undergo transplacental transmission.[14,18–20] Although fewer than 20 case reports exist in the literature, transplacental transmission has been documented. Affected infants generally have poor outcomes, and a majority succumbs to disease during the first year of life. However, there have been rare isolated cases of spontaneous regression.[14,18–20] All pigmented lesions in neonates born to mothers with melanoma should be evaluated to rule out transplacental transmission. Previously, this determination relied on fluorescent in situ hybridization (FISH), but more recent reports have established the utility of PCR-based genotyping to confirm transplacental metastasis.[18] A thorough gross and histologic examination of the placenta should be performed postpartum in all women with a history of malignant melanoma, as placental metastases have been described in even early stage melanoma.[14,18]

Predisposition syndromes

Genetic disorders that affect tumor suppressor genes such as p53, cause alterations in the cell cycle, or that render the cell more sensitive to DNA damage are associated with a greater risk of melanoma. The best described of these syndromes is xeroderma pigmentosum (XP), an autosomal recessive disorder affecting DNA repair after UV exposure. XP patients are exquisitely sensitive to UV damage with 5–13% developing melanoma by age 21 years. Additionally, most patients with XP will develop a non-melanoma skin cancer by age 8 years.[5,14] Sun protection and early detection of skin lesions are essential in these children.

Dysplastic nevi syndrome, which can occur sporadically or in a familial form, is another recognized predisposition syndrome. These children will have multiple nevi by 5 years of age and will develop dysplasia throughout adolescence. Mutations in the *CDKN2A* (cyclin-dependent kinase 2A) locus and the *CDK4* gene have been implicated in this syndrome, particularly in the setting of >100 nevi, and in nevi located on the buttocks and feet.[5,14] The *CDKN2A* mutation has been associated with multiple primary melanomas and an elevated pancreatic cancer risk.[5,14] Other germline mutations (*BAP-1, BRCA2,* and *MC1R*) have been associated with adult melanoma.[14] Additional investigation is required before pediatric recommendations regarding genetic testing or screening can be made. At a minimum, since the total number of nevi and atypical nevi are independent risk factors for melanoma, these children should be followed closely by clinical exam.[10]

Finally, immunosuppression is a well-documented risk factor for melanoma. Children with immunodeficiency syndromes have a sixfold increase in the risk of melanoma development. Children with acquired immunodeficiency syndromes such as those undergoing organ transplantation, chemotherapy for malignancy, and human immunodeficiency syndrome (HIV) have a three to fourfold increase in risk.[5,10] Undergoing maintenance chemotherapy alone may increase the number of melanocytic nevi in children.[10,21] All immunosuppressed children should undergo routine skin examination as part of their ongoing monitoring.

Histopathology

The diagnosis of melanoma in children and adolescents should be made by an experienced dermatopathologist. Critical histopathologic features include Breslow thickness of the lesion, presence or absence of histologic ulceration, dermal mitotic rate, peripheral and deep margin status of the biopsy, and microsatellitosis.[22] In children, the diagnosis of melanoma is complicated by lesions in which the growth pattern or cytology may differ minimally from a benign nevus. This histologic uncertainty was recognized as early as 1948, when Sophie Spitz first described the overlap of certain histopathologic features of unequivocally benign nevi and malignant melanoma in children.[23] Although these benign Spitz nevi were recognized as a distinct entity with no malignant potential, other lesions sharing characteristics of Spitz nevi, but deviating from the typical growth pattern caused uncertainty among even expert dermatopathologists. These lesions, termed “atypical spitzoid lesions” have most of the characteristics of unequivocally benign Spitz nevi but also possess some atypical features.[10,14] Sentinel lymph node biopsy (SLNB) has been utilized in attempts to distinguish which of these lesions may have malignant potential, but results from small case series have been mixed, especially with regard to patient prognosis, and this practice is not currently recommended.[10,24–26]