Catherine Hickson. *Morning Table*. Oil on Belgian linen, 123 cm × 183 cm.

Melanoma incidence in children has increased in the United States over the last few decades, and continued study is needed to improve early diagnosis, biopsy protocols, therapies, and outcomes.

Pediatric Melanoma: A Review

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Background: *Malignant melanoma is a rare neoplasm in the pediatric population, but its incidence has risen in recent years.*

Methods: *The literature was reviewed to define the current clinical and pathologic features of pediatric melanoma, highlighting the similarities and differences between adult and pediatric melanoma.*

Results: *Distinctive features of this disease, including frequency and type of genetic abnormalities, predisposing conditions, clinical presentation, stage at diagnosis, prognostic features, and frequency of sentinel lymph node positivity are emphasized. Treatment strategies, extrapolated from adult melanoma trials, are also discussed.*

Conclusions: *Despite the differences between pediatric and adult melanoma, survival rates are similar and are improving in both populations. Further studies will help delineate the pathogenesis of both adult and pediatric melanoma, with the goal of contributing to early detection and improved survival.*

Epidemiology

Pediatric melanoma is generally defined as melanoma occurring in patients ranging in age from in utero to 21 years, although the upper limits of the cutoff age vary from 13 to 21 years in published reports.[1] Pediatric melanoma can be subdivided into several groups including congenital (in utero to birth), neonatal or infantile (birth to 1 year), childhood (1 year to puberty), and adolescent melanoma (puberty to 21). Each subgroup has an increased incidence of one or more melanoma precursor lesions that is fairly distinct to the age group. Melanoma in the pediatric age group accounts for 1% to 4% of all cases of melanoma and for 1% to 3% of all pediatric malignancies.[2] A rise in the incidence of pediatric melanoma has become apparent as databases more accurately record the incidence of these rare malignancies.[2] From 1973 to 2001, the incidence of pediatric melanoma increased 2.9% per year (95% confidence interval [CI], 2.1–3.6) and 46% (95% CI, 40–52) per year of age.[1,3,4] According to a report from the US Surveillance, Epidemiology and End Results Program, approximately 300 to 420 new pediatric cases of melanoma are diagnosed each year.[5,6] Lewis[7] found that from 1968 to 2004 in the United States, an average of 18 deaths per year were attributed to melanoma in children 20 years of age and younger. In a review of the National Cancer Database, overall

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childhood melanoma is slightly more common in girls (55%), although boys slightly predominate in the younger age groups (1 to 4 years).[8] In a study of 3,158 patients with melanoma aged 1 to 19 years, 3.8% were 1 to 4 years, 5.7% were 5 to 9 years, 17.3% were 10 to 14 years, and 73.2% were 15 to 19 years.[8]

Pathogenesis and Genetic Mechanisms

Primary melanoma evolves from melanocyte transformation directly or in precursor lesions in both genetically normal and predisposed patients. While not yet fully elucidated, melanoma tumorigenesis likely represents a multistep process involving accumulation of sequential genetic alterations, including oncogene activation, tumor suppressor gene inactivation, and impaired DNA repair.[9] The best-characterized genetic mutations, discussed below, have been mostly described in adult melanoma but also appear to be important for the development of pediatric melanoma. These mutations involve the CDKN2A/retinoblastoma (Rb) gene and p53 pathways, the melanocortin-1 receptor, and the RAS/RAF/MAP kinase pathway.

Hereditary melanoma was first described by Clark et al[10] and Lynch et al,[11] whose separate reports described kindreds with familial melanoma and clinically atypical moles. Subsequent genetic studies showed linkage to markers on chromosome 9p21, where germline mutations in the CDKN2A gene are now known to reside in 25% to 50% of patients with familial melanoma. The CDKN2A locus codes for two proteins: p16/INK4a and p14/ARF (alternative reading frame). The proteins are tumor suppressors that are involved in critical pathways of growth regulation and apoptosis via Rb and p53 pathways, respectively.[12] Affected patients develop melanoma earlier in life than nonaffected individuals, although not in childhood. CDKN2A mutations were found in a smaller percentage (1.6%) of childhood melanoma compared with adult melanoma (10%).[5]

Less commonly, germline mutations are found in cyclin-dependent protein kinase 4 (Cdk4), a locus that genetically interacts with CDKN2A. Cdk4 is normally inhibited by p16/INK4A, but mutant Cdk4 is resistant to p16 and therefore functions as an autosomal dominant oncogene. Affected individuals have the same phenotype as those with germline p16 mutations.[12]

Another genetic locus linked to melanoma predisposition is also associated with fair skin color, red hair, and freckling — the melanocortin-1-receptor (MC1R). MC1R is expressed on the melanocyte surface and is a receptor for a melanocyte-stimulating hormone, binding of which leads to a switch from red/yellow pheomelanin to brown/black eumelanins.[13] MC1R mutants have a 2.2- to 16-fold increased risk of melanoma. It has also been found that MC1R variants are associated with increased CDKN2A penetrance.[12] Box et al[14] studied 15 Australian CDKN2A mutation-carrying melanoma pedigrees and assessed them for the MC1R genotype. In patients with a CDKN2A mutation without MC1R variant mutation, the penetrance was 50%. However, when an MC1R variant allele was also present, the penetrance increased to 84% with a reduction in the mean age of melanoma onset from 58.1 to 37.8 years ($P = .01$).[14]

BRAF is a component of the RAS/RAF/MAP kinase signal transduction pathway, mutations of which are found in both nevi and subtypes of melanoma occurring in sun-exposed skin. In keeping with the multistep model of melanogenesis, an interesting association of MC1R variants and BRAF-mutant melanomas has been recently observed. Specifically, melanomas arising in patients with MC1R variant alleles are significantly more likely to harbor BRAF mutations,[15] irrespective of the presence of the melanoma on sun-damaged or non–sun-damaged skin.[16]

A pediatric-specific pathogenetic finding is described in a recent study by Uribe et al.[9] Loss of heterozygosity (LOH) of tumor DNA in pediatric and adult melanoma was compared. The authors also used microsatellite techniques to show allelic loss in tumors compared with normal tissue. Higher levels of microsatellite instability (MSI) and LOH were found in pediatric melanoma compared with adult melanoma, although the differences did not reach statistical significance. Higher frequencies of allelic loss at 11q23 were found in pediatric melanoma, postulated to be related to its early onset. High-frequency MSI found in pediatric melanoma could increase the rate of spontaneous mutations in both oncogenes and tumor suppressor genes leading to tumorigenesis. High-frequency LOH in the loci of TP53, RB1, and BRCA1 genes in both adult and pediatric melanoma could reflect inactivation of these genes and a role in melanoma pathogenesis.

Risk Factors and Predisposing Conditions

While genetic alterations predisposing to melanoma are currently under investigation, many risk factors for melanoma are well documented. Factors consistently shown to confer an increased risk of developing melanoma include a family history of melanoma, history of severe sunburns (> 3 before the age of 20 years), marked freckling on the upper back, light hair color, immunosuppression, and a higher number of nevi.[17]

Livestro et al[18] found a family history of melanoma was more common in young patients, although the difference did not reach statistical significance: 25.6% of pediatric patients had a positive family history compared with 17.3% of adults.

The role of sunlight in the development of melanoma is well established. Sun-specific risk factors include number of sunburns, especially obtained during childhood, and cumulative exposure to UV radiation. Compared with the general population, patients with xeroderma pigmentosum, an autosomal recessive disorder caused by a genetic defect in DNA repair after

damage by UV radiation, are 2,000 times more likely to develop melanoma.[17] This disorder is discovered in the first or second year of life with marked photosensitivity or freckling.

Other predisposing conditions include immunosuppression and a previous history of malignancy.[1,5,19-21] Immunosuppression secondary to a hematologic, infectious, or acquired disorder (organ or bone marrow transplant) increases the pediatric patient's risk of melanoma 3- to 6-fold.[2] The number of pediatric melanoma cases arising in these predisposing conditions suggests a stronger predisposing genetic component operant in pediatric melanoma cases.

Role of Melanocytic Nevi

Perhaps the most distinct risk factor for pediatric melanoma is its relationship with pre-existing melanocytic nevi. Livestro et al[18] found histologically identifiable precursor nevi were more likely in young patients with melanoma than in adults.

Congenital Melanocytic Nevi: In a review of melanocytic lesions associated with 324 pediatric melanomas, 11% were found to develop in congenital nevi, and 6% were found to develop in acquired nevi.[5] In another study, large congenital melanocytic nevi were found in 33% of prepubertal melanomas, a significant difference from their frequency of association with adult melanoma.[22]

Congenital melanocytic nevi (CMN) occur in approximately 1 in 20,000 newborns, and their risk for development of melanoma increases with size.[23] Small (< 1.5 cm) and medium CMN (1.5 to 19.9 cm) carry a lifetime risk of malignant transformation of 2% to 5%, while giant (> 20 cm) congenital melanocytic nevi (GCMN) carry a 4.5% to 10% lifetime risk.[24,25] The cellular location and age of incidence of melanoma occurring in a congenital nevus precursor also vary with the size of nevus. Specifically, melanomas developing in small to medium CMN generally begin to arise at or around puberty and continue to arise throughout adult life. In these nevi, the melanoma develops at the dermoepidermal junction as melanoma in situ. Due to the relative frequency of CMN, the number that transforms into melanoma is difficult to establish.[24] Malignant transformation is a relatively common occurrence in GCMN: 50% to 70% of these lesions develop melanoma, generally before 10 years of age. Malignant transformation of GCMN generally occurs in the deep dermal component of the lesion rather than in the dermoepidermal junction.[25,26]

Because of their close relationship with pediatric melanoma, a brief discussion of the management of congenital nevi is warranted. While the optimal management of congenital nevi is controversial, it is generally accepted that complete excision of the entire lesion in early childhood decreases the risk of malignancy. The conundrum is that this is difficult to accomplish in those lesions of highest risk, and removal of the more frequent, smaller, and lower risk lesions in early childhood may pose undue psychological trauma as well as cosmetic consequences. Often, excision of the largest lesions is accomplished by serial excision using tissue expanders.[27] Another option is close monitoring by physical examination with serial follow-up and prompt excision if the lesion changes.[2]

Dysplastic Nevi: Dysplastic nevi are markers of increased clinical risk for the development of melanoma. The dysplastic nevus syndrome (familial mole-melanoma syndrome), an autosomal-dominant disorder wherein patients develop hundreds of dysplastic nevi, is associated with an increased risk of melanoma, within both nevi and normal skin. Diagnostic criteria include multiple dysplastic nevi and two family members with melanoma.[28] Dysplastic nevi are found in 5% to 10% of the US population. One case-control study of 716 patients with melanoma demonstrated that one clinically dysplastic nevus conferred a 2-fold increase in the risk of developing melanoma and that 10 or more conferred a 12-fold increased risk.[29] In a study of 844 patients from 33 families with two or more members having invasive melanoma, there were 86 new cases of melanoma among 37 individuals over a follow-up period of 2 to 25 years.[30] Fifty-one of the 86 cases had a precursor lesion. Of these 51 precursor lesions, 32 were dysplastic nevi.[5] The same group found that 37% of children of melanoma-prone families had dysplastic nevi and that the only children to develop pediatric melanoma were those with dysplastic nevi. These children were diagnosed with melanoma at a younger age than average: 9% of cases developed before 20 years of age. This study found a reduction in the age at diagnosis of melanoma in successive generations, from 50 years in the first generation to 12 years in the fourth generation.

Common Nevi: The role of common (nondysplastic) nevi in the development of pediatric melanoma is somewhat controversial. Numerous epidemiologic studies of patients of all age groups have demonstrated that the total number of melanocytic nevi on the body is the strongest risk factor for the development of melanoma.[31] Of the various types of nevi, it has been demonstrated that the number of common nevi is the strongest independent indicator of an increased risk for the development of melanoma, followed by the number of atypical nevi, and then by solar lentigines (also known as age or liver spots).[32] This is likely due to the interplay between sun exposure and the development of common nevi, as it has been shown that the incidence of these lesions increases rapidly during childhood as a result of sun exposure.[31] The number of nevi is also directly related to the patient's phenotype. One study showed that both the number and density of nevi increased in a linear fashion between 6 and 12 years of age.[33] The number and density of nevi

increased at a greater rate for boys than girls, for patients with blue, hazel, or green eyes compared to brown, and for blonde- vs dark-haired individuals.

It does not appear that common nevi (nevi "not otherwise specified") are significantly more frequent in the pediatric melanoma patient. A case-matched controlled analysis compared the biology of pediatric and adult melanoma by matching adult melanoma patients by tumor thickness and year of diagnosis to a population of young melanoma patients.[2] In a comparison of precursor lesions, the percentage of nevi "not otherwise specified" was similar in the adult (20%) and pediatric (26%) patients.

Clinical Presentation of Pediatric Melanoma

Diagnosing melanoma in a child is often challenging for a variety of reasons. The majority of melanomas in the pediatric population arise de novo.[2,34] In addition, many clinicians may have a low index of suspicion while unaware of risk factors and predisposing conditions in young patients. The presentation of pediatric melanoma can be quite nonspecific; lesions may resemble a benign nevus, dysplastic nevus, hemangioma, Spitz nevus, pyogenic granuloma, or verruca.[35] In an early series of 125 patients with pediatric melanoma, the most common clinical presentations included increasing size of a mole, bleeding, color change, itching, palpable adenopathy, and palpable subcutaneous mass.[36] Compared with adult melanoma, a significant proportion of pediatric melanomas are amelanotic (50%) and have a nodular configuration (30%). Compared with adults, melanoma in children presents at a greater median thickness (3.5 mm).[37] This is likely due to physicians' hesitancy to biopsy children, resulting in a delay in diagnosis and often inadequate biopsy specimens and thus hindering effective pathologic evaluation. Nonwhite children are disproportionately represented in the pediatric melanoma population,[8] especially in cases occurring in children under 10 years of age.

Downard et al[2] note that the initial physical examination of a patient with a cutaneous lesion should include a thorough evaluation of the entire skin surface with special attention to additional suspicious lesions. Mucus membranes, the digits, and interdigital spaces should be examined carefully. Photography may be helpful if lesions are being followed over time. The traditional ABCD criteria of melanoma (asymmetry, border irregularity, color, and diameter > 6 mm) are helpful in evaluation of the suspicious lesion being considered for biopsy, although these criteria may not be as universally applicable in children as they are in adults.[2,38]

Table 1. — Classification of Pediatric Melanoma by Mode of Occurrence

1. Transplacental melanoma, transmitted from the mother with melanoma to the fetus in utero.
2. Transformation from giant congenital melanocytic nevus.
3. In association with congenital predisposing conditions such as xeroderma pigmentosum, dysplastic nevus syndrome, and albinism.
4. Development from healthy skin.
5. Development from a preexisting nevus.

Histopathologic Classification

Because pediatric melanoma can arise from conditions unique to the young, pediatric melanoma can be classified by its mode of occurrence (Table 1), as well as by the traditional histologic subtypes.[2,39] Transplacental melanoma is exceedingly rare. In a recent review, 27 patients were reported to have melanoma involving the placenta or fetus from 1918 to 2002.[40] Microscopic evaluation of the placenta was performed in 24 of these patients, and involvement was documented in all of

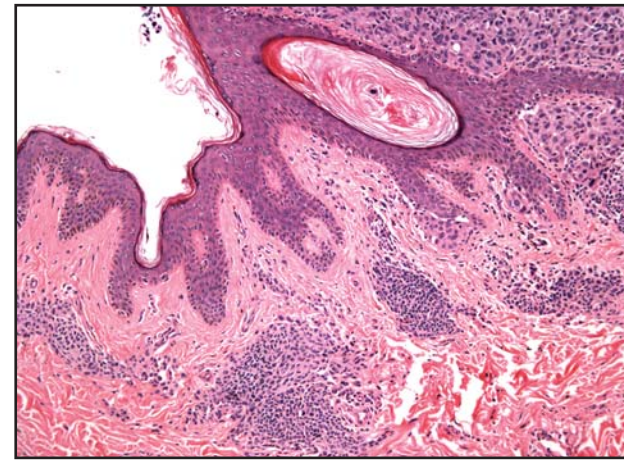

Fig 1. — Melanoma arising at dermoepidermal junction of small congenital nevus (hematoxylin-eosin, × 200).

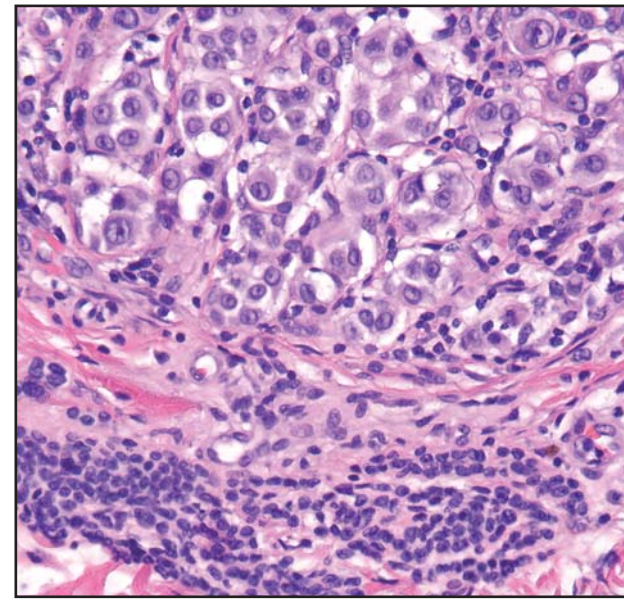

Fig 2. — Melanoma arising in dermal component of large congenital nevus (hematoxylin-eosin, × 400).

them. Six of the 27 reports indicated the presence of fetal metastasis. Eight of the 27 (29%) newborns with placental involvement died, 3 of prematurity and 5 of widespread melanoma. Sixteen showed no evidence of disease at a mean follow-up of 14.2 months, 2 of whom had signs of metastatic melanoma (cutaneous melanosis in 1 and proven lung metastases in 1) that regressed.

With the exception of melanoma arising in congenital nevi, melanoma arising de novo in children is histologically identical to that of adults. Specifically, melanoma arising in small congenital nevi typically arises at the dermoepidermal junction (Fig 1), while large congenital nevi tend to manifest malignant transformation in the dermal component (Fig 2). Of the four histologic subtypes, superficial spreading melanoma is the most common type in both pediatric and adult patients.[2] Young patients appear to have a greater frequency of minimal deviation melanoma (a melanocytic tumor with histologic features intermediate between benign nevi and malignant melanoma with a clinically benign course) and nodular melanoma. Pediatric melanomas showed a general absence of the lentigo maligna subtype, suggesting sun exposure plays a less important role in the development of melanoma in young individuals.[18]

Evaluation of biopsies by an experienced dermatopathologist is essential. Features that distinguish malignant tumors from benign lesions in the differential diagnosis include the following: a gradual transition zone into the normal epidermis at the lateral edge of the melanocytic proliferation as opposed to sharply demarcated melanocytic proliferations at the epidermal lateral margin, extreme degrees of melanocytic hyperplasia in both lentiginous and nested patterns, pagetoid spread of individual and clustered melanocytes throughout the epidermis, destruction of epidermal cells by proliferating cells resulting in epidermal erosion or ulceration, and asymmetrical lesional architecture in the dermis secondary to foci of expansile dermal masses of cells and patchy inflammatory regression. Anaplastic melanocytic atypia with cellular pleomorphism and bizarre nuclear features are to be distinguished from reactive features seen in benign lesion. Features that are also noted in malignant lesions include loss of maturation at the base of the lesion, asymmetric inflammatory (usually lymphocytic) host response with accompanying melanophages, dermal fibrosis, and telangiectasia.[41]

Differential Diagnoses

The differential diagnosis of melanoma includes Spitz nevus, cellular and sclerotic blue nevus, and congenital nevus with proliferative nodule (Table 2). Spitz nevi are important historically since this entity, originally thought to represent melanoma in children and adolescents, was associated with a better prognosis than in adults until the delineation of its histopathologic features resulted in the ability to distinguish between this benign entity and melanoma.[42] Also known as spindle and epithelioid cell nevus and as benign juvenile melanoma, the Spitz nevus typically occurs in children and adolescents. Spitz nevi are considered benign melanocytic neoplasms. The classic Spitz nevus is dome-shaped and symmetric with abrupt attenuation of the junctional nests at the lateral borders of the lesion. The nevus is composed of differing amounts of spindle and epithelioid melanocytes. Spindle cells are usually arranged in vertically oriented nests, whereas epithelioid cells are dispersed individually throughout the lesion. Lesions may be wedge-shaped, and nevus cells mature by becoming smaller as they descend into the dermis. Melanocyte nuclei may be large and irregular in contour and may contain prominent eosinophilic nucleoli. Mitot-

Table 2. — Differential Diagnoses of Pediatric Melanoma

	Melanocytes	Shape/Borders	Background	Distinctive Features
Spitz Nevus	Spindled cells in vertical nests; epithelioid cells dispersed throughout	Dome-/wedge-shaped; symmetric, well-circumscribed	Kamino bodies at dermoepidermal junction; cellular uniformity	Maturation of cells with descent into the dermis; large irregular nuclei with prominent nucleoli; mitotic figures; pagetoid epidermal spread
Blue Nevus: Dendritic	Spindled dendritic cells occupying dermis	Dome-shaped; well-circumscribed	Melanophages with melanin pigment	No cellular atypia, necrosis, or mitotic activity
Blue Nevus: Cellular and Sclerotic	Dendritic and ovoid uniform melanocytes	Lobulated, circumscribed inferior border with periadnexal growth, extension into deep dermis, occasionally subcutaneous fat	Occasional dermal sclerosis	Encystification may occur in large lesions and simulate necrosis, mitotic rate < 2/mm^2
Congenital Nevus With Proliferative Nodule	Expansile cellular masses of monomorphic cells	Cells within nodule blend with surrounding melanocytes of nevus	Large congenital nevus	Lack of necrosis and junctional activity; gradual regression with time; mitoses up to 10/mm^2

ic figures and pagetoid epidermal spread of melanocytes may also mimic melanoma. Unique histologic features include the deposition of eosinophilic globules of hyaline-like material near the dermal-epidermal junction (Kamino bodies), although the majority of cells appear uniform, and this background of benignity helps to differentiate the Spitz tumor from melanoma (Fig 3).[43] However, melanomas can mimic Spitz nevi and are referred to as Spitzoid melanoma or melanoma with Spitz nevus-like features. In these lesions, the melanocytic proliferation, though similar to Spitz nevus, have predominant features of melanoma and are broad, poorly circumscribed, and asymmetrical. Features of Spitzoid melanoma include abundant pagetoid spread, high-grade nuclear atypia, high mitotic rate with deep dermal mitoses or atypical mitoses, no or focal maturation at the base, deep penetration into the lower dermis or subcutis, ulceration, and large lesional size. Some neoplasms share features of both Spitz nevi and Spitzoid melanoma. This borderline group of tumors has an indeterminate malignant potential and is designated atypical Spitz tumor (Fig 4).[44] Sentinel node biopsy may be helpful in evaluation of these patients (discussed below).

Blue nevi are dermal proliferations of spindle melanocytes that occur in three forms: common (dendritic), cellular, and sclerotic. Common blue nevus is a benign dome-shaped lesion often occurring on the hands and feet. Histologic examination reveals a well-circumscribed dermal lesion with melanin pigment deposition, predominately in melanophages in a background of spindled, dendritic, and delicate dermal melanocytes that may occupy the entire dermis and extend into subcutaneous fat. Both cellular and sclerosing blue nevus may mimic melanoma histologically, while the common blue nevus does not. Cellular blue nevi are frequently deep, involving subcutaneous fat, and possess cellular areas that may undergo a peculiar type of degeneration that resembles necrosis (encystification).[45] They may have mitotic activity, although it is usually low. While cellular blue nevus may progress to melanoma, common and sclerosing blue nevi do not.[46]

Congenital nevi may undergo changes that are both benign and malignant. Proliferative nodules are areas of rapid growth within the dermal component of congenital nevi that may cause a rapid change in size or ulceration of the nevus.[47] These growths can simulate melanoma both clinically and histologically, but they are benign. They occur most commonly in giant congenital nevi and occur in the dermal component. Proliferative nodules are pathologically characterized by expansile, cellular masses of monomorphous melanocytes, often with high mitotic activity of up to 10 mitoses per high-power field (Fig 5).[48] Because of these features, there is a suspicion that they may be overdiagnosed as melanoma. Features useful in establishing a benign diagnosis include the blending of cells at the periphery of the nodules with the surrounding nevus, lack of necrosis, and lack of junctional activity.[48] The natural history of proliferative nodules is one of gradual diminution in size, softening, and/or complete regression. Recently, comparative genomic hybridization has been performed on a proliferative nodule arising in a large congenital nevus to assess its malignant potential.[47] The finding of a normal karyotype led the authors to conclude it was most likely benign since only 4% of melanomas have a normal karyotype.

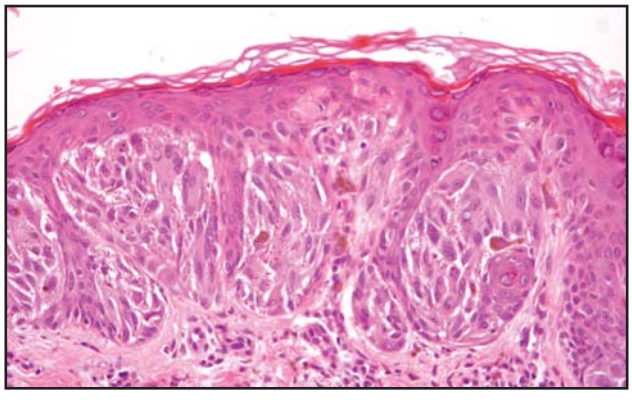

Fig 3. — Spitz tumor without atypia (hematoxylin-eosin, × 400).

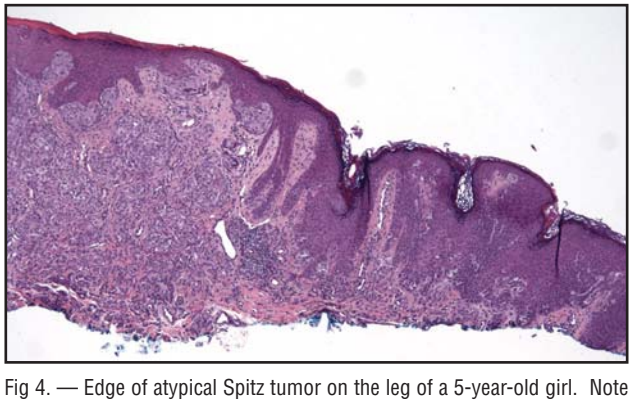

Fig 4. — Edge of atypical Spitz tumor on the leg of a 5-year-old girl. Note poor circumscription and asymmetry (hematoxylin-eosin, × 100).

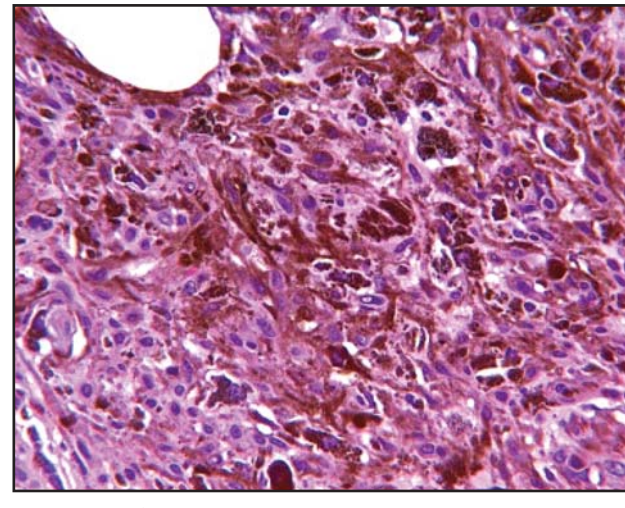

Fig 5. — Proliferative nodule within giant congenital melanocytic nevus (hematoxylin-eosin, × 200).

Diagnostic Techniques/Role of Sentinel Node Biopsy

Lesions clinically suspicious for melanoma should be biopsied as completely as possible. While full-thickness excisional biopsy is recommended, this is not always feasible in the office setting since heavy sedation or even general anesthesia is often necessary to perform this procedure in the pediatric population.[2] Children diagnosed with melanoma undergo wide local excision with the width of the circumferential margins determined by tumor depth as in adults: recommended margins are 0.5 to 1 cm for melanoma in situ lesions, 1 cm for lesions less than 1 mm in thickness, and 2 cm for all other lesion thicknesses.[2,49]

Sentinel node biopsy has become a standard practice in staging regional lymph nodes in adult patients with melanoma, and there is now consensus that this procedure should be offered to pediatric patients. A number of recent studies have reported a consistently higher rate of sentinel lymph node involvement in pediatric patients compared with adults. In five recent series, the incidence of positive sentinel nodes ranged from 25% to 60% of patients, with a median tumor thickness of 1.65 to 4.17 mm,[50-54] an incidence substantially higher than in adults. The tendency for children to have greater overall tumor thickness at presentation may partly explain this phenomenon. To answer this question, one of the largest recent series compared the biology of pediatric and adult melanoma with the use of an adult control group that was matched for tumor thickness.[18] Of the patients < 20 years of age who underwent pathologic staging of clinically negative lymph nodes, 44% had positive lymph nodes compared with 23.9% of the adults, suggesting lymph node metastases are more prevalent in young patients with melanoma compared with adults. However, due to the small sample size, this difference did not reach statistical significance.

The guidelines for performing sentinel lymph node biopsies in children are the same as those in adults. A biopsy is warranted for lesions thicker than 1 mm and the presence of ulceration or a Clark level of invasion of IV or V, or mitotic activity in patients with lesions less than 1 mm.[5,55] In general, if melanoma cells are found in the sentinel lymph nodes, complete lymph node dissection of the basin is offered to the patient.

Current diagnostic techniques for pediatric and adult melanoma patients are the same. However, it is unclear if both sentinel lymph node biopsy and complete lymph node dissections confer a survival advantage to either pediatric or adult patients with melanoma.[2]

Sentinel lymph node biopsies are often advocated in pediatric patients with diagnostically challenging lesions. The most common lesion in this diagnostically challenging arena are those resembling Spitz nevus with atypical features (so-called atypical Spitz tumor). These lesions of uncertain biologic potential, if found to demonstrate metastatic deposits in sentinel lymph nodes, are then considered to represent melanoma based on the premise that only melanoma will metastasize to the sentinel lymph nodes. Several recent publications have addressed this issue.[56-61] In these series, a total of 23 (41%) of 56 patients with Spitzoid melanocytic lesions of uncertain biologic potential demonstrated deposits of tumor cells in sentinel lymph nodes. However, this may not always be the case in the setting of atypical lesions since benign melanocytic lesions have been reported to involve lymph nodes.[52] Thus, completion lymphadenectomy for "metastatic" deposits of atypical lesions is controversial.

Adjuvant Treatment

Because of the rarity of pediatric melanoma, accruing adequate numbers of patients for clinical trials to evaluate adjuvant therapy is difficult. Therefore, the treatment of children is often based on information gleaned in adult studies. Currently, interferon alfa-2b is the biological agent of choice. Adult studies have shown that adjuvant treatment of high-risk melanoma with high-dose interferon for 4 weeks, followed by low-dose treatment for 48 weeks, results in improvement in recurrence-free survival when compared with observation.[62-64]

A recent prospective trial of adjuvant interferon treatment was conducted for 15 patients with stage III pediatric melanoma.[65] Of these 15 patients, 9 completed the therapy and 2 recurred during therapy. Pediatric patients suffered less toxicity than adults, mainly neutropenia.

Another recent report examined the use of high-dose interferon in 6 pediatric melanoma patients with metastatic disease on sentinel lymph node biopsy.[51] Five of 6 underwent complete lymph node dissection followed by high-dose interferon treatment. Four of the 5 completed treatment and were in remission at the completion of the study with a median of 26 months follow-up, and 1 was still receiving treatment. Dose adjustments were required in a significant number of patients: 2 for myelosuppression and 2 for abnormal liver function tests.

In summary, while the impact of this treatment on recurrence and survival remains to be determined, it is feasible to offer interferon to pediatric patients.

Prognosis

Overall survival for all patients with pediatric melanoma appears to be similar to that of adults. In the previously noted study comparing 73 pediatric melanoma patients to 146 thickness-matched adult patients, 5-year (91.3% and 86.2%) and 10-year (89.4% and 79.3%) disease-specific survival was similar between the two groups, respectively,[18] with a median follow-up of 5.4 and 4.6 years. There appears to be no difference in survival between pediatric patients < 13 years of age compared to those between 13 to 20 years.[18]

Another large study with shorter follow-up, focusing on patients with positive sentinel nodes, found differences in recurrence and survival despite the significantly higher incidence of nodal positivity in children. Roaten et al[66] reported sentinel lymph node metastases in 8 (40%) of 20 patients aged 12 to 20 years compared with 55 (18%) of 307 adults with a median follow-up of 35 and 17 months for the groups, respectively. No sentinel lymph node-positive pediatric patients recurred, but 14 (25%) adults recurred within this period and 5 (9.1%) died of disease.

Poor prognostic factors in adults include increased primary lesion thickness, ulceration, non-extremity site, increased age, regional lymph node involvement, satellite or in-transit metastases, elevated serum lactate dehydrogenase level, and visceral or brain metastases.[1,67,68] Unfavorable prognostic factors in children include male sex (mortality rates are 25% higher than females),[7] regional or distant metastasis, nodular histology, increasing thickness of primary, primary of the head, face, neck, eye, orbit, central nervous system, genitals, or overlapping sites, earlier year of diagnosis, and a history of previous cancer.[1] Younger children are more likely to have poor prognostic features including metastasis, thick primaries, high-risk histology, and a history of cancer.

Conclusions

The incidence of pediatric melanoma is rising, and though no decrease in pediatric melanoma thickness at presentation has been noted in the last 10 years,[1] the mortality from melanoma among children in the United States is falling.[7] Survival in children has improved by approximately 4% per year in the United States during the last 3 decades.[1] This may be associated with primary preventive measures such as the adoption of sun-safe practices. Secondary prevention such as earlier detection, better diagnostic tools (dermoscopy), and improved access to dermatologic services also may have contributed. This trend was consistent across gender (males, females) and racial groups (white, black, other).[7] While pediatric melanoma and adult melanoma have distinctive differences, diagnostic techniques and sentinel lymph node biopsy guidelines remain the same. Treatment with interferon is acceptable based on adult trials and recent pediatric studies. Continued studies of both adult and pediatric melanoma may further delineate the pathogenesis of pediatric melanoma, contribute to early tumor diagnosis, and outline sentinel lymph node biopsy protocols and adjuvant treatment therapies to increase survival from this important childhood malignancy.

References

1. Strouse JJ, Fears TR, Tucker MA, et al. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. *J Clin Oncol*. 2005;23(21):4735-4741.
2. Downard CD, Rapkin LB, Gow KW. Melanoma in children and adolescents. *Surg Oncol*. 2007;16(3):215-220. Epub 2007 Oct 31.
3. Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992-2004). *Cancer*. 2008;112(2):416-432.
4. Fisher DE, Medrano EE, McMahon M, et al. Meeting report: fourth international congress of the Society for Melanoma Research. *Pigment Cell Melanoma Res*. 2008;21(1):15-26.
5. Pappo AS. Melanoma in children and adolescents. *Eur J Cancer*. 2003;39(18):2651-2661.
6. Pappo A, Ries L, Herzog C, et al. Malignant melanoma in the first three decades of life: a report from the U.S. Surveillance, Epidemiology and End Results (SEER) Program. *J Clin Oncol, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition)*. 2004;22(14S July 15 suppl):7557. Abstract.
7. Lewis KG. Trends in pediatric melanoma mortality in the United States, 1968 through 2004. *Dermatol Surg*. 2008;34(2):152-159. Epub 2007 Dec 17.
8. Lange JR, Palis BE, Chang DC, et al. Melanoma in children and teenagers: an analysis of patients from the National Cancer Data Base. *J Clin Oncol*. 2007;25(11):1363-1368.
9. Uribe P, Wistuba II, Solar A, et al. Comparative analysis of loss of heterozygosity and microsatellite instability in adult and pediatric melanoma. *Am J Dermatopathol*. 2005;27(4):279-285.
10. Clark WH Jr, Reimer RR, Greene M, et al. Origin of familial malignant melanomas from heritable melanocytic lesions. 'The B-K mole syndrome'. *Arch Dermatol*. 1978;114(5):732-738.
11. Lynch HT, Frichot BC 3rd, Lynch JF. Familial atypical multiple mole-melanoma syndrome. *J Med Genet*. 1978;15(5):352-356.
12. Lin J, Hocker TL, Singh M, Tsao H. Genetics of melanoma predisposition. *Br J Dermatol*. 2008;159(2):286-291. Epub 2008 Jun 28.
13. Rouzaud F, Kadekaro AL, Abdel-Malek ZA, et al. MC1R and the response of melanocytes to ultraviolet radiation. *Mutat Res*. 2005;571(1-2):133-152. Epub 2005 Jan 26.
14. Box NF, Duffy DL, Chen W, et al. MC1R genotype modifies risk of melanoma in families segregating CDKN2A mutations. *Am J Hum Genet*. 2001;69(4):765-773. Epub 2001 Aug 8.
15. Landi MT, Bauer J, Pfeiffer RM, et al. MC1R germline variants confer risk for BRAF-mutant melanoma. *Science*. 2006;313(5786):521-522. Epub 2006 Jun 29.
16. Hacker E, Hayward NK. Germline MC1R variants and BRAF mutant melanoma. *J Invest Dermatol*. 2008;128(10):2354-2356.
17. Markovic SN, Erickson LA, Rao RD, et al. Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis. *Mayo Clin Proc*. 2007;82(3):364-380.
18. Livestro DP, Kaine EM, Michaelson JS, et al. Melanoma in the young: differences and similarities with adult melanoma. A case-matched controlled analysis. *Cancer*. 2007;110(3):614-624.
19. Kraemer KH, Lee MM, Andrews AD, et al. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer: the xeroderma pigmentosum paradigm. *Arch Dermatol*. 1994;130(8):1018-1021.
20. Tucker MA, Goldstein AM. Melanoma etiology: where are we? *Oncogene*. 2003;22(20):3042-3052.
21. Whiteman DC, Valery P, McWhirter W, et al. Risk factors for childhood melanoma in Queensland, Australia. *Int J Cancer*. 1997;70(1):26-31.
22. Trozak DJ, Rowland WD, Hu F. Metastatic malignant melanoma in prepubertal children. *Pediatrics*. 1975;55(2):191-204.
23. Fishman C, Mihm MC Jr, Sober AJ. Diagnosis and management of nevi and cutaneous melanoma in infants and children. *Clin Dermatol*. 2002;20(1):44-50.
24. Marghoob AA. Congenital melanocytic nevi: evaluation and management. *Dermatol Clin*. 2002;20(4):607-616, viii.
25. Ruiz-Maldonado R, del Rosario Barona-Mazuera M, Hidalgo-Galván LR, et al. Giant congenital melanocytic nevi, neurocutaneous melanosis and neurological alterations. *Dermatology*. 1997;195(2):125-128.
26. Ruiz-Maldonado R, Orozco-Covarrubias ML. Malignant melanoma in children. A review. *Arch Dermatol*. 1997;133(3):363-371. Review. Erratum in: *Arch Dermatol*. 1997;133(7):833.
27. Chung C, Forte AJ, Narayan D, et al. Giant nevi: a review. *J Craniofac Surg*. 2006;17(6):1210-1215.
28. Greene MH, Goldin LR, Clark WH Jr, et al. Familial cutaneous malignant melanoma: autosomal dominant trait possibly linked to the Rh locus. *Proc Natl Acad Sci U S A*. 1983;80(19):6071-6075.
29. Tucker MA, Halpern A, Holly EA, et al. Clinically recognized dysplastic nevi: a central risk factor for cutaneous melanoma. *JAMA*. 1997;277(18):1439-1444.
30. Goldstein AM, Fraser MC, Clark WH Jr, et al. Age at diagnosis and transmission of invasive melanoma in 23 families with cutaneous malignant melanoma/dysplastic nevi. *J Natl Cancer Inst*. 1994;86(18):1385-1390.
31. Bauer J, Garbe C. Acquired melanocytic nevi as risk factor for melanoma development: a comprehensive review of epidemiological data. *Pigment Cell Res*. 2003;16(3):297-306.
32. Garbe C, Büttner P, Weiss J, et al. Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the Central Malignant Melanoma Registry of the German Dermatological Society. *J Invest Dermatol*. 1994;102(5):695-699.

33. Milne E, Simpson JA, English DR. Appearance of melanocytic nevi on the backs of young Australian children: a 7-year longitudinal study. *Melanoma Res*. 2008;18(1):22-28.
34. Jafarian F, Powell J, Kokta V, et al. Malignant melanoma in childhood and adolescence: report of 13 cases. *J Am Acad Dermatol*. 2005;53(5): 816-822. Epub 2005 Sep 29.
35. Ceballos PI, Ruiz-Maldonado R, Mihm MC Jr. Melanoma in children. *N Engl J Med*. 1995;332(10):656-662.
36. Boddie AW Jr, Smith JL Jr, McBride CM. Malignant melanoma in children and young adults: effect of diagnostic criteria on staging and end results. *South Med J*. 1978;71(9):1074-1078.
37. Ferrari A, Bono A, Baldi M, et al. Does melanoma behave differently in younger children than in adults? A retrospective study of 33 cases of childhood melanoma from a single institution. *Pediatrics*. 2005;115(3):649-654.
38. Bono A, Ferrari A. Early diagnosis remains the most reliable way to cure children with melanoma. *Pediatr Blood Cancer*. 2005;45(3):355; author reply 356.
39. Richardson SK, Tannous ZS, Mihm MC Jr. Congenital and infantile melanoma: review of the literature and report of an uncommon variant, pigment-synthesizing melanoma. *J Am Acad Dermatol*. 2002;47(1):77-90.
40. Alexander A, Samlowski WE, Grossman D, et al. Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. *J Clin Oncol*. 2003;21(11):2179-2186.
41. Mills SE, Carter D, Greenson JK, et al eds. *Sternberg's Diagnostic Surgical Pathology*. 4th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2004.
42. Spitz S. Melanomas of childhood. 1948. *CA Cancer J Clin*. 1991; 41(1):40-51.
43. Celebi JT, Messina JL. Challenging melanocytic neoplasms: spitzoid melanoma vs spitz nevus. In: Agarwala SS, Sondak VK, eds. *Melanoma: Translational Research and Emerging Therapies*. New York, NY: Informa Healthcare USA, Inc; 2008.
44. Barnhill RL. The Spitzoid lesion: rethinking Spitz tumors, atypical variants, 'Spitzoid melanoma' and risk assessment. *Mod Pathol*. 2006;19 (suppl 2):S21-33.
45. Cerroni L, Borroni RG, Massone C, et al. "Ancient" blue nevi (cellular blue nevi with degenerative stromal changes). *Am J Dermatopathol*. 2008;30(1):1-5.
46. Barnhill RL, Argenyi Z, Berwick M, et al. Atypical cellular blue nevi (cellular blue nevi with atypical features): lack of consensus for diagnosis and distinction from cellular blue nevi and malignant melanoma ("malignant blue nevus"). *Am J Surg Pathol*. 2008;32(1):36-44.
47. Murphy MJ, Jen M, Chang MW, et al. Molecular diagnosis of a benign proliferative nodule developing in a congenital melanocytic nevus in a 3-month-old infant. *J Am Acad Dermatol*. 2008;59(3):518-523. Epub 2008 Jul 21.
48. Leech SN, Bell H, Leonard N, et al. Neonatal giant congenital nevi with proliferative nodules: a clinicopathologic study and literature review of neonatal melanoma. *Arch Dermatol*. 2004;140(1):83-88.
49. Thomas JM, Newton-Bishop J, A'Hern R, et al. Excision margins in high-risk malignant melanoma. *N Engl J Med*. 2004;350(8):757-766.
50. Bütter A, Hui T, Chapdelaine J, et al Melanoma in children and the use of sentinel lymph node biopsy. *J Pediatr Surg*. 2005;40(5):797-800.
51. Shah NC, Gerstle JT, Stuart M, et al. Use of sentinel lymph node biopsy and high-dose interferon in pediatric patients with high-risk melanoma: the Hospital for Sick Children experience. *J Pediatr Hematol Oncol*. 2006;28(8):496-500.
52. Pacella SJ, Lowe L, Bradford C, et al. The utility of sentinel lymph node biopsy in head and neck melanoma in the pediatric population. *Plast Reconstr Surg*. 2003;112(5):1257-1265.
53. Roaten JB, Partrick DA, Pearlman N, et al. Sentinel lymph node biopsy for melanoma and other melanocytic tumors in adolescents. *J Pediatr Surg*. 2005;40(1):232-235.
54. Toro J, Ranieri JM, Havlik RJ, et al. Sentinel lymph node biopsy in children and adolescents with malignant melanoma. *J Pediatr Surg*. 2003; 38(7):1063-1065.
55. Sondak VK, Taylor JM, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. *Ann Surg Oncol*. 2004;11(3):247-258.
56. Durrani AJ, Moir GC, Diaz-Cano SJ, et al. Malignant melanoma in an 8-year-old Caribbean girl: diagnostic criteria and utility of sentinel lymph node biopsy. *Br J Dermatol*. 2003;148(3):569-572.
57. Gamblin TC, Edington H, Kirkwood JM, et al. Sentinel lymph node biopsy for atypical melanocytic lesions with spitzoid features. *Ann Surg Oncol*. 2006;13(12):1664-1670.
58. Gurbuz Y, Apaydin R, Muezzino lu B, et al. A current dilemma in histopathology: atypical spitz tumor or Spitzoid melanoma? *Pediatr Dermatol*. 2002;19(2):99-102.
59. Lohmann CM, Coit DG, Brady MS, et al. Sentinel lymph node biopsy in patients with diagnostically controversial spitzoid melanocytic tumors. *Am J Surg Pathol*. 2002;26(1):47-55.
60. Su LD, Fullen DR, Sondak VK, et al. Sentinel lymph node biopsy for patients with problematic spitzoid melanocytic lesions: a report on 18 patients. *Cancer*. 2003;97(2):499-507.
61. Urso C, Gelli R, Borgognoni L, et al. Positive sentinel node biopsy in a 30-month-old boy with atypical Spitz tumour (Spitzoid melanoma). *Histopathology*. 2006;48(7):884-886.
62. Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol*. 1996;14 (1):7-17.
63. Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol*. 2001;19(9):2370-2380.
64. Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res*. 2004;10(5):1670-1677.
65. Navid F, Furman WL, Fleming M, et al. The feasibility of adjuvant interferon alpha-2b in children with high-risk melanoma. *Cancer*. 2005; 103(4):780-787.
66. Roaten JB, Partrick DA, Bensard D, et al. Survival in sentinel lymph node-positive pediatric melanoma. *J Pediatr Surg*. 2005;40(6):988-992; discussion 992.
67. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001; 19(16):3622-3634.
68. Ahmed I. Malignant melanoma: prognostic indicators. *Mayo Clin Proc*. 1997;72(4):356-361.