Melanoma in Children

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The rate of malignant melanoma incidence has been rising rapidly in recent years. Patients under the age of 20 years account for approximately 2% of all melanomas, and prepubertal children make up 0.3 to 0.4% of all cases.[1,2] Malignant melanoma, the most common fatal skin cancer, is seven times more frequent in the second than the first decade of life. It predominantly affects Caucasian children with nearly equal occurrence in both sexes.[2] Frequently, there is a significant lag in the diagnosis of melanoma in children.[2] Due to its rising incidence, increased awareness of melanoma in childhood is mandatory. This review will discuss melanomas in children, as well as its predisposing factors.

Congenital Malignant Melanoma

The occurrence of congenital malignant melanoma is rare, but may be seen in any of four distinct situations. 1) The most commonly occurring scenario is that of congenital melanoma resulting from maternal melanoma metastasis via the placenta. The infant often dies due to multiorgan involvement.[2,3] These lesions appear as black, small macules and nodules that are occasionally ulcerated, or as palpable subcutaneous masses. 2) Rapidly expanding, ulcerated, and bleeding 1- to 3-cm black nodules may be found in congenital melanoma arising *de novo in utero*, in which there is no indication of pre-existing maternal malignancy.[2] 3) *In utero* development of melanoma may occur in a giant pigmented nevus; it is usually fatal within a few months of birth. This lesion commonly appears as ulcerated and nonulcerated black nodules of varying size on the surface of a giant nevus or occasionally on an area of normal skin.[2] 4) Prenatal melanoma can arise in the existing nevi of neurocutaneous melanosis,

FIGURE 1. Congenital melanocytic nevus.

which is characterized by the concurrent presence of giant pigmented nevi, or >3 congenital nevi, with leptomeningeal melanosis.[2,4] These nevi are commonly found on the scalp or middle aspect of the back.[3] Congenital melanoma arising in neurocutaneous melanosis is most often found in Caucasians and follows a rapidly fatal course.[2]

Primary Cutaneous Melanoma

Forty percent to 50% of melanomas in children are primary cutaneous melanomas.[2] These melanomas appear as unevenly pigmented macules, of various hues of red or blue intermixed with shades of white, brown, or black. Primary malignant melanoma most frequently afflicts the head and trunk of males while predominantly appearing on the arms and legs of females.[2]

The differential diagnosis of similar-appearing lesions in children can be quite extensive, including Reed nevi; traumatized common, congenital, or acquired nevi; dysplastic nevi; blue nevi; spindle and epithelial cell (Spitz) nevi; pyogenic granulomas;

traumatized verrucae; hemangiomas; thrombosed lymphangiomas; seborrheic keratoses; and pigmented basal cell carcinomas.[2] Most of these can be readily differentiated by histologic examination of a biopsy specimen.[2] However, the atypical Spitz nevus often poses a significant problem when attempting to distinguish it from a malignant melanoma. Misdiagnosis of a melanoma as a spitz nevus, or vice versa, commonly occurs due to the numerous histologic features shared by the two lesions.[5] Distinction between the two is further complicated by the notion that Spitz nevi exhibit histologic features that range from completely benign to malignant.[6] A grading system has recently been proposed to assist in the classification of malignant potential.[7] Parameters include patient age, diameter, fat involvement, ulceration, and mitotic activity.

Congenital Melanocytic Nevi

Clinical Description—The congenital melanocytic nevus (CMN) is present at birth or soon after, and is found in 1% of all newborns.[8] These benign neoplasms appear as light or dark macules or papules that are sometimes covered with hair [9] (Figure 1). These nevi may significantly change in color and have increased hair growth as the child matures, often becoming plaques or nodules with the development of a verrucous surface. CMN is predominantly found on the trunk and thighs, with frequent appearance on the face and extremities. Occasionally these lesions may be found on the scalp, palms, or soles. CMN are categorized as small (<1.5 cm), medium (1.5 to 19 cm), and giant (≥20 cm) lesions.[10] Giant melanocytic nevi (GCMN) occur in approximately 1 of 20,000 newborns.[11] One of 500,000 babies is born with the massive "garment" or "bathing trunk" nevus, which cloaks an entire back, a large area of the trunk, or an extremity.[12]

Potential for Malignant Degeneration and Management — The increased risk of malignant transformation in small- and medium-sized congenital melanocytic nevi is widely disputed.[13] A recent study reinforced the opinion that benign-appearing medium-sized CMN are not at a substantially increased risk of malignant transformation.[14] This finding is consistent with the belief that mandatory prophylactic excision of medium melanocytic nevi is not necessary, and that life-long observation is an acceptable method of management. Similarly, another study has recently reported no additional risk of melanoma in medium- or small-sized melanocytic nevi.[15]

Others, however, report that even small melanocytic nevi carry an increased risk of transformation into malignant melanoma. It has been reported that the risk of malignancy in these nevi be-

comes greatest after puberty, with estimations of 0.8 to 4.9% cumulative risk for melanoma occurrence in patients living up to 60 years of age.[2] Some recommend prophylactic excision, while others suggest no intervention unless atypical features are found.

Conversely, there is a consensus on the status of giant congenital melanocytic nevi as melanoma precursors. It is estimated that at least one-third of all prepubertal melanomas arise from these lesions.[16] These lesions occur primarily in females and are covered by hair in greater than 95% of patients.[17] GCMN, and nevi covering more than 5% of skin surface area, are associated with a 1000-fold increase in the risk of melanoma mortality.[2] A number of studies on giant CMN have demonstrated incidences of melanoma ranging from 1.8 to 7.1%.[18-22] Additionally, ample evidence suggests that malignant transformations commonly occur prior to puberty, most frequently before the age of six.[16,23] A recent review supports this notion, demonstrating that roughly one-half of all GCMN-associated melanomas may occur prior to 3 to 5 years of age, with a 5.7% cumulative risk.[24] Additional findings in this study include increased melanoma risk with advancing patient age and size of nevus, as well as frequent appearance of the melanoma on truncal lesions.

Malignant transformation typically begins deep in the nevus; thus, surface changes are usually not observed until late in the development of melanoma.[25] This makes early detection extremely difficult, and metastasis is often already present at the time of diagnosis. Accordingly, management of giant CMN should concentrate on prophylactic excision.[8]

Removal of the entire lesion is often arduous due to its sheer size. A number of techniques are used to circumvent this dilemma. A promising advancement in this area involves the use of tissue expanders to significantly increase the size of the normal skin surface area that can be used for closure.[26] Another method used by DeMey *et al*[27] involved the curettage of CMN with better cosmetic outcome than other techniques used. Additionally, a substantial portion of nevus cells are located in the epidermis. Thus, serial shaving of this layer facilitates observation and early detection.[28] However, this technique probably does not guarantee the elimination of malignant transformation because nevus cells may remain in deeper tissue. In fact, surgical removal encroaching on the fascia does not completely eliminate this risk. Up to two-thirds of melanomas in GCMN originate from layers deep to the epidermis.[2] Also, melanomas may arise in these patients from clinically normal skin; melanoma may still develop even if all clinically apparent nevi are excised.[14,20,23] Therefore, frequent examination of these patients is imperative.

Associated Syndromes—CMN is associated with numerous syndromes and retains a comparable increased risk of melanoma as those found occurring in isolation. These disorders include NAME (Nevi, Atrial myxoma, Myxoid neurofibroma, Ephelides) syndrome, LAMB (Lentignes, Atrial myxoma, Mucuocutaneous myxoma, Blue nevi) syndrome, Carney syndrome, Noonan's syndrome, premature aging and short stature syndrome, and, as mentioned previously, neurocutaneous melanosis.[25]

Non-CMN Pediatric Melanoma Precursors

Acquired Atypical Nevi—In adults, risk factors for melanoma include fair skin, lightly pigmented eyes, childhood history of blistering sunburn, and increased counts of typical and atypical nevi.[29-32] However, whether these same risk factors bear a comparable amount of significance in the development of childhood melanoma has not been established.[12,33] Regardless, an increased number of nevi have been found in children with light skin, hair, and eyes.[34] Thirty-five children characterized as having a "Celtic" complexion were reported in a study of 121 children with melanomas unlinked to congenital lesions.[1] In comparison to melanomas developing in CMN, the incidence of melanoma occurrence abruptly increased at puberty and continued this trend through young adulthood. However, an indeterminate number of these children may have suffered from dysplastic nevus syndrome (see below).

In children, the clinical appearance of malignant degeneration of an acquired nevus is the same as in adults. The signs and symptoms of malignant transformation include the onset of bleeding or pruritus, as well as changes in size, shape, or color of the nevus. It is imperative that physicians observe these changes and take immediate action. Reluctance to consider melanoma in a child may lead to a delay in diagnosis, and has been connected to decreased survival in up to 60% of cases.[35]

Other Nevi—One must consider the potential of malignant transformation in other types of nevi, although these are uncommon occurrences.[2] There are a small number of reports describing the malignant transformation of blue nevi in children. Although there are documented cases of melanoma arising in cellular blue nevus and nevus spilus, both of which may be congenital, the rates of these occurrences are unknown. Finally, the nevus of Ota, which is associated with leptomeningeal melanoma, has a minute potential to act as a precursor to melanoma.[2,3]

Dysplastic Nevus Syndrome—Dysplastic nevi are potential melanoma precursors, and may sometimes indicate an increased risk of melanoma development in other areas.[36,37] These 5- to 10-mm macules or papules are often tan, brown, pink, or black with unclear or irregular borders. Exact parameters defining dysplastic nevus syndrome have not been established. However, most agree that there is a familial melanoma syndrome associated with numerous atypical nevi. Several studies have indicated association with chromosome 1 with autosomal dominant inheritance.[38] Furthermore, increased nevus count is more strongly correlated with the risk of melanoma development than positive family history or clinical appearance of individual nevi.[39,40]

The occurrence of dysplastic nevi in prepubertal children is not infrequent. Notably, there are reports of melanoma occurring in children as young as 10 years of age.[41] More typically, multiple "normal-appearing" melanocytic nevi are found on 5- to 6-year-old children with dysplastic nevis syndrome. These nevi do not exhibit dysplastic traits until puberty has been reached, often with initial involvement of the scalp.[2,12] A recent study of children revealed that a substantial number of dysplastic nevi of the scalp and forehead have definite atypical features.[42] The importance of examination of the scalp for these lesions should be stressed.

Currently, precise management of affected children has not been established. Children with a small number of stable nevi may be examined yearly after receiving a baseline evaluation, and, ideally, photography of existing lesions. More frequent examinations should be performed on those with a positive personal or family history, large number of nevi, or nevi that appear to be changing. Early malignant degeneration is probably best indicated by the development of a new area of black pigmentation.[43]

Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is characterized by abnormal cellular repair of DNA damaged by ultraviolet radiation.[44] The development of photosensitivity or significant freckling at 1 to 2 years of age is often the first manifestation of XP in a child.[2,45] These children rapidly develop numerous basal and squamous cell carcinomas, with 5% of patients developing melanoma.[2,45] A 1994 study showed that approximately one-half of melanomas in XP males occur on the face, head, and neck, with other prevalent sites including the trunk and upper extremities.[46] Females also develop melanomas in those same areas with the addition of a 33% occurrence in the lower extremities. Meticulous observation, frequent inspections, and vigorous protection from the sun are crucial in these patients.

Immunosuppression

Children who are genetically immunodeficient have a three- to sixfold increased risk of developing melanoma.[47] Iatrogenic immunosuppression and human immunodeficiency virus infection also pose an increased risk of melanoma development in affected children.[48,49] In addition, an increased nevus count and induction of atypical nevi have been reported in children who receive chemotherapy for malignant neoplasms and in those who receive immunosuppression after renal transplantation.[2] Dysplastic nevi in immunosuppressed patients should be managed aggressively with prompt prophylactic excision of lesions.[12]

Prevention

The implementation of simple measures may prevent many casses of melanoma. Patients should be educated on the dangers of the sun since melanoma often affects skin that receives periodic, intense sun exposure.[2,3] The avid use of broad-spectrum (UVA and UVB) sunscreens should also be discussed, with explicit instructions detailing their utilization. In a recent study, increased development of nevi was found in Caucasian, European children who used sunscreen, probably because it promotes increased recreational sun exposure.[50] Patients must be warned that sunscreen use does not imply unlimited time in the sun and that the sunscreen must be reapplied every 2 to 3 hours. The authors of this study suggest that children simply wear more clothing.

It is important that physicians recognize pediatric conditions that are associated with an increased risk of melanomas in childhood. Detection of structural resonance in congenital nevocellular nevi by computerized image analysis of histopathologic sections offers important prospects for the future.[51]

Treatment

The first step in treatment of a diagnosed melanoma is excision of the primary site. Regional lymph node resection should be performed when there is clinical suspicion of involvement.[2] There is an ongoing investigation into the use of lymphatic mapping, which may provide a means of assessing those cases that need additional therapy as well as expedite accurate staging of the disease.[52] In addition to surgical excision, other therapeutic regimens for melanoma include chemotherapy, radiotherapy, and immunotherapy.[2]

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