HANDOUT
Clinical, histologic, and immunohistochemical features in melanomas of childhood and adolescence.
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Victor G. Prieto, MD, PhD.
Departments of Pathology and Dermatology. The University of Texas M.D. Anderson Cancer Center, Houston, TX (USA).

This companion meeting will be focused on neoplastic lesions in children and adolescents. On the field of melanocytic lesions, this first lecture will focus on the clinical, histological, and immunohistochemical findings of melanocytic lesions, and it will be followed by two lectures describing the most recent developments in the fields of molecular pathology (CGH, FISH, and proteomics).

Cutaneous melanoma in childhood is rare, particularly before puberty. The incidence under 15 years of age is approximately 1 per million (7% of cancers among patients aged 15-19 years vs. 1.2% in patients younger than 15 years of age).

As with adult population, childhood melanoma mainly affects Caucasian individuals; some series have indicated that white race is associated with an impaired prognosis, although that is not our experience. Some studies have suggested that there is a slight female predominance and that male sex is associated with worse prognosis. However our experience, of the data from cancer registry show equal sex distribution and prognosis. The extremities and the trunk are the most common anatomic locations for cutaneous melanomas in children. On the other hand it has been suggested that childhood melanomas arising from the head and neck may have worse prognosis.

Like in the adult population, the most likely reason to suspect melanoma is the detection of changes in the appearance of a “mole”. Changes described in decreasing order of frequency are: rapid size increase, bleeding, color change, itch, lymph node enlargement, subcutaneous mass, pain and distant metastases. Another common presentation is that of an amelanotic lesion. Approximately 10% of melanomas develop in association with a pre-existing nevus are asymptomatic. Since a diagnosis of melanoma is only rarely included in the differential diagnosis of cutaneous lesions in children, some studies have reported that up to 50-60% of cases have had a significant delay in the diagnosis.

Only a minority of childhood melanoma in children may also occur in mucosal surfaces. Primary melanomas of mucosal sites (oral and nasal cavity, genitourinary, gastrointestinal and conjunctiva) account for only 3-4% of all melanomas.

Many of known risk factors associated with melanoma in adults (e.g., large congenital nevi, dysplastic nevus syndrome, numerous nevi) may be also identified during childhood. Such conditions were demonstrated in about 50% of cases. As in adults, a large number of melanocytic nevi in children are associated with increased risk of melanoma and a number of childhood melanomas arise in either congenital or acquired nevi. There is some controversy about the risk for progression of congenital nevi to melanoma. Historical estimates of melanoma risk were likely exaggerated due to diagnosis of proliferative nodules as developing in congenital nevi as melanoma. Regarding malignant transformation of congenital nevi, approximately 10% of childhood melanoma arises from congenital nevi, including 3.5% from giant nevi. In our experience, approximately half of all childhood melanomas arise in children with sporadic dysplastic nevi and around 10% in children with dysplastic nevus syndrome. In general, familial cases account for approximately 5-10% of melanomas. This antecedent greatly increases risk of melanoma, both for patients with
dysplastic and benign nevi. Familial melanoma is associated with a lower age at diagnosis than sporadic melanoma, presence of dysplastic nevi and the development of multiple primary melanomas. The pattern of heredity is consistent with an autosomal dominant inheritance with incomplete penetrance. Inactivating mutations of the CDKN2A gene (for p16 and p14ARF) are present in 20-40% of such families and in 15% of individuals with multiple primary melanomas but only rarely (less than 5%) of childhood melanomas. In our series 15 (22.4%) patients had 3 or more first-degree relatives with melanoma, but none of them had multiple melanomas during the follow-up.

Another phenotype associated with melanoma is the presence of large number of melanocytic nevi. In a study of 201 adolescents with melanoma, they reported a 34-fold increased risk in patients with more than 100 nevi and 15-fold in those with 10 or more large nevi. In our series we found such association only in 21% of patients.

A precursor nevus has been reported in up to 47% of childhood melanomas although it appears that the percentage is much lower (15%). Small congenital nevi occur in 1% of newborns, and rarely develop melanoma before the second decade of life. In our large series, we only found small nevi in 2/137 patients (3%). On the other hand, it is interesting that we have shown that children in whom the melanoma is associated with a benign melanocytic nevus have a significantly lower risk of metastases.

Other risk factors include inherited and acquired immunodeficiency. In pediatric population, melanoma account for up to 15% of all post-transplantation skin cancers. Regarding sun exposure, unless the patient suffers from inherited conditions that increase sensitivity to ultraviolet light, such as xeroderma pigmentosum, it is unlikely that sun-exposure will be associated with childhood melanoma.

Survivors of childhood cancer have increased risk for a second neoplasm, including melanoma. Such lesions tend to be deeper and have poor prognosis, possibly associated with tumor-related immunodeficiency mechanisms mediated by the neoplasm itself.

The most important finding regarding prognosis is age. In most studies, older age, likely after puberty, is associated with worse survival. In several series, the large majority patients who died from melanoma were older than 10 years at time of diagnosis. For example, Sander et al reviewed 126 cases of melanoma in young patients, and found that all 13 deceased patients were older than 12 years of age. It is also our experience, since in our series all our patients who died from melanoma were older than 10 years at time of diagnosis. Thus it seems that postpuberal age is one of the main factors determining death risk.

**Histology:**

In general, it seems that the same histopathologic criteria developed for adult melanoma should be used for diagnosis of childhood melanoma: size >10 mm, asymmetry, lateral borders poorly demarcated, intraepidermal pagetoid spread of single cells prominent in the center or else present at the periphery of the lesion, irregular intraepidermal nest formation, “consumption”/atrophy or ulceration of the epidermis, absence of maturation, deep extension in dermis/subcutaneous tissue, expansive deep border, expansive / diffuse sheets of cohesive cells in the dermis, cellular atypia, and deeply located or atypical mitotic figures. However, these features should be evaluated together since none of them is sufficient for a diagnosis of melanoma.

Regarding histologic subtypes, several series have reported a predominance of nodular lesions, but more recent series indicate that most childhood melanomas are of superficial spreading type. It is possible that some of the cases in prior series were actually superficial spreading melanomas with large, dermal, nodular component. It is interesting that some
studies have indicated that true nodular morphology is associated with impaired prognosis. Interestingly, in contrast with melanomas in adults, in whom histologic subtype is not related to prognosis, nodular melanomas appear to show poor survival in children. There appear to be higher rate of metastases in melanomas with fusiform or spitzoid cytology. Also, some studies have indicated impaired prognosis of lesions with melanomas of small cell type, similar to small round cell tumors.

A high percentage of reported childhood and adolescent melanomas are relatively thick, possibly due to delay in suspicion of malignancy. When comparing adult and pediatric melanomas, the latter show significantly thicker tumors and such thicker lesions appear to have poor prognosis. Nodal metastases have been detected in up to 2/3 of children with Clark level IV-V or Breslow >1.5 mm melanomas. Conversely, metastases or recurrence are unusual in patients with melanoma <1.5 mm thick. As in adults, ulceration, VGP, vascular invasion and high mitotic activity are also associated with higher recurrence rate, although in our experience it did not correlate with decreased survival. Brisk lymphocytic infiltrate and regression do not appear to have significant correlation with survival.

The most challenging diagnosis is the subtype spitzoid melanoma. There appears to be a spectrum of lesions from obvious benign (i.e., Spitz nevus) to obvious malignant (spitzoid melanoma), with a group of lesions falling in between the two poles of the spectrum. It has been reported that up to 40% of melanomas originally diagnosed as nevi actually correspond to these spitzoid melanomas.

Classic Spitz nevus is considered as a benign lesion with some nuclear and cytological pleomorphism but absence of deep/atypical mitotic figures, expansile pattern of growth, etc. (see above). In contrast, spitzoid melanoma is a malignant melanocytic lesion with some cytological attributes of Spitz nevus (spindle and/or epithelioid melanocytic cells) but with a preponderance of the atypical features summarized above. Patients with lesions sharing some classic features of Spitz nevus and some of these abnormal pathology features, in which a definite diagnosis of nevus or melanoma is not firmly established, may be described as atypical spitzoid lesions or atypical Spitz tumors (of unknown biological potential).

The term “nevoid melanoma” applies to lesions in which there is little proliferation of melanocytes in the epidermis and a dermal proliferation that mimics some features of a compound or intradermal nevus. Due to the lack of prominent intraepidermal component some of these lesions are diagnosed as nevi. The main histological features to look for in these lesions include: dermal mitotic figures, sheet-like growth pattern, nuclear pleomorphism and lack of conventional maturation (monomorphous appearance of the melanocytes throughout the lesion.

Although the diagnosis of melanoma continues to rest on microscopic morphologic features, immunohistochemistry may be helpful in a number of cases, especially in like spitzoid or nevoid melanoma. HMB-45 usually shows a stratified pattern with diminished expression toward the base of the lesion (maturation) in most nevi, including Spitz nevi, in contrast with the patchy pattern of expression throughout melanomas. Blue nevi, deep penetrating nevi, plexiform nevi, and a minority of Spitz nevi show diffuse labeling with HMB45. Spitz nevi also have low proliferation rates (1-2%) when assessed with Ki-67, compared with much higher rates in melanomas (15-30%). Moreover, melanoma has labelling throughout the lesion while nevi have more staining at the top of the lesion than at the bottom (maturation). S100 protein and MART-1 (melanoma antigen recognized by T cells-1) show diffuse expression throughout both Spitz nevus and melanoma; however, desmoplastic melanomas may lose MART1 expression while preserving S100; this finding may be diagnostically helpful. Any spindle cell melanocytic lesion that shows either patchy or negative expression of MART1 should be carefully evaluated to rule out melanoma.
Other markers have been studied in spitzoid and other childhood melanocytic lesions. p16 and its related protein CDK4 show a mostly inverse pattern of expression; many Spitz nevi express p16 but not CDK4 and the opposite is true for melanoma. However, more recent studies question the usefulness of immunohistochemical analysis of p16 to distinguish Spitz nevus from spitzoid melanoma.

Expression of CD133, a stem-cell marker, has been reported to be associated with aggressive behavior (lymph node and visceral metastasis) in childhood melanoma.

During the period 1968-2004, there were 643 deaths attributed to melanoma among children aged 0-19 years in US (2.25/year/million at-risk individuals). We have shown that presence of metastases at the time of diagnosis is one of the two main factors that influence overall survival in children with melanoma. Along these lines, it has been reported that pediatric patients have a survival at 10 years of with 94.5% in stage I-II and 60.1% in stage III.

Regarding sentinel lymph node (SLN), recent studies indicate that this procedure has a less significant predictive value in childhood melanomas than in adult lesions. While approximately 20% of melanomas in adults are associated with positive SLN, pediatric lesions show values between 25 and 60. This seems to indicate that even with positive SLN, those children appear to have a better prognosis than adults. Although it is unclear why, it have been suggested possible differences in lymphatic flow density and immune system, which would be able to clear micrometastases in children. Another possibility is that some of these positive SLN actually contain benign melanocytes (nodal nevi). These nodal nevi are usually small clusters of benign-appearing melanocytes within the capsule (and rarely in the parenchyma) of lymph nodes, in contrast with the common subcapsular location of metastatic melanoma. Overall, up to 20% of lymphadenectomies from the axilla or groin contain such benign collections of melanocytes. These benign nodal melanocytes usually lack gp100 expression (with HMB45), and show very low Ki67 expression, thus consistent with benign melanocytes. In order to facilitate the identification of proliferating melanocytes, it is possible to use a cocktail that includes anti-MART1 and MIB1 (against Ki67). Since these two markers are expressed in different cellular components (Ki67 in the nucleus and MART1 in the cytoplasm) it is relatively easy to determine how many of the melanocytes (i.e., cells expressing MART1) are proliferating (i.e., expressing Ki67). In view of the apparent differences between prognostic information derived from SLN examination in children and adults, only long-term follow-up studies will be able to determine the actual value of SLN in melanocytic lesions from children.

In conclusion, careful analysis of histological features as well as the additional immunohistochemistry should allow establishing the right diagnosis in most cases of childhood melanoma. Although it seems that pediatric melanoma patients still a number of children will develop metastasis and die of their disease, particularly when melanoma is diagnosed after puberty.

References: