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Controversies in the Evaluation and Management of Atypical Melanocytic Proliferations in Children, Adolescents, and Young Adults

Damon Reed, MD^{a,b}, Ragini Kudchadkar, MD^b, Jonathan S. Zager, MD^b, Vernon K. Sondak, MD^b, and Jane L. Messina, MD^{c,d}

^aDepartment of Sarcoma Oncology, Moffitt Cancer Center, University of South Florida, Morsani College of Medicine, Tampa, Florida.

^bDepartment of Cutaneous Oncology, Moffitt Cancer Center, University of South Florida, Morsani College of Medicine, Tampa, Florida.

^cDepartment of Dermatology, University of South Florida, Morsani College of Medicine, Tampa, Florida.

^dDepartment of Pathology and Cell Biology, University of South Florida, Morsani College of Medicine, Tampa, Florida.

Abstract

The rising incidence of melanoma in children has brought increased attention to the clinical and pathologic diagnosis of pigmented lesions in the pediatric age group. Although melanoma in infancy and early childhood is often associated with large congenital nevi, in older children and teenagers it is most often sporadic, occurring in patients with a low skin phototype and substantial sun exposure. The rarity of this potentially fatal disorder demands astute clinical attention and a high index of suspicion for atypical lesions in pediatric patients. The challenges include the difficult decision of whether to biopsy and an often equivocal pathologic diagnosis. These diagnostically challenging and equivocal lesions lead to a degree of uncertainty regarding additional workup, prognosis, potential therapy, and follow-up plans. Consultation with a specialty dermatopathologist can be very helpful, and advanced molecular diagnostic techniques may be used in selected circumstances. Although still controversial, good evidence exists to justify a role for sentinel lymph node biopsy. Patients with atypical melanocytic proliferations have a high rate of positive sentinel lymph nodes; however, their outcomes are clearly better than in similarly staged adults with conventional melanoma. With the multiple variables involved and the relative lack of prospectively derived evidence, clinical decision-making is challenging and patients and families may experience considerable stress. This article provides data and weighs the pros and

Correspondence: Damon Reed, MD, Sarcoma Department, Moffitt Cancer Center, 12902 Magnolia Drive, FOB 1, Tampa, FL 33612. Damon.Reed@moffitt.org.

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cons of a rationale for decision-making in pediatric and young adult patients with diagnostically challenging melanocytic lesions.

Although melanoma in children remains rare, constituting 1% to 3% of pediatric malignancies, its incidence is increasing.^{1,2} There is often a low suspicion, with an average time to diagnosis of up to 9 months in reported series.³ The number of nevi resected per melanoma diagnosis is much higher in children than in adults (nearly 600:1; 20 times higher than in adults).⁴ Further differences in the pediatric population include a significantly higher incidence of diagnostically challenging lesions, a higher rate of regional lymph node involvement, and seemingly better outcomes than adults with similarly staged melanomas.^{4,5} Many strides have been made in elucidating the pathogenesis of melanoma in adults, resulting in efficacious targeted and immune therapies for metastatic disease; however, children younger than 18 years have been excluded from most of these studies.^{6,7} Melanoma management in adults has become better defined as results of randomized trials have shown clear survival benefits with newer agents; however, the data on pediatric patients are minimal and treatment is often based in extrapolation from those from adults.

Compounding the challenges of managing pediatric melanoma is the increasing recognition that many melanocytic proliferations in childhood demonstrate pathologic features showing significant overlap with both benign and malignant lesions. These diagnostically challenging lesions have been given a variety of confusing acronyms and appellations, including Spitzoid tumor of uncertain malignant potential (STUMP),⁸ melanocytic tumor of uncertain malignant potential (MELTUMP),⁹ superficial atypical melanocytic proliferation of uncertain significance (SAMPUS),⁹ atypical Spitz tumor (AST),¹⁰ and atypical melanocytic proliferation (AMP).¹¹ AMP is the term the authors prefer. Many AMPs bear a resemblance to benign melanocytic proliferations, especially Spitz, deep penetrating, and cellular blue nevi (Table 1, Figure 1).

No reliable method exists to predict the natural history of AMPs. Furthermore, AMPs do not seem to represent a distinct subset of melanocytic neoplasm, either clinically or pathologically. In many cases, lesions initially diagnosed as AMP on biopsy are reclassified as melanoma based on features only seen in the reexcision specimen, or even once metastases develop. The reports of adverse outcomes, even death, in patients diagnosed initially with AMPs, especially those with Spitz nevus-like features, prompt careful, measured consideration in making this diagnosis.^{12,13} Although the occurrence of AMPs is not limited to pediatric (<12 years old), adolescent (12–18 years old), and young adult (18–39 years old) patients, they are most common in these age groups. This article attempts to highlight current clinical controversies surrounding AMPs in pediatric/young adult patients and provide a rational process to aid clinical decision-making.

Presentation

An early series of more than 100 pediatric patients with melanoma identified what were believed to be common presentations, including increasing size of or changing color within a mole, pruritus, and/or palpable adenopathy.¹⁴ Compared with adults, nonwhite children are overrepresented and a greater proportion of the pediatric population has amelanotic

lesions ($\approx 50\%$).¹⁵ Nodular lesions also occur at a greater frequency in pediatric ($\approx 30\%$) versus adult melanoma.¹⁶ Congenital nevi are often a source of melanoma development in pediatric patients. Approximately one-third of prepubertal melanomas arise from large congenital nevi, and 50% of melanomas arising from large congenital nevi occur in patients younger than 10 years.^{14,17} In a collection of retrospective reviews reporting associations between melanoma and congenital nevi, 45 of 693 (6.4%) of patients had a congenital nevus preceding the diagnosis.¹⁸ Xeroderma pigmentosa, a disorder of nucleotide excision repair rendering affected patients exquisitely sensitive to ultraviolet damage, can lead to melanoma in 5% to 13% of patients before their twentieth birthday.^{19,20} Familial melanoma remains incompletely understood, but accounts for 5% to 10% of pediatric melanoma cases. Mutations in CDKN2A can lead to multiple and recurrent melanomas but are present in fewer than 5% of childhood melanomas.¹⁹ Atypical/dysplastic nevi raise melanoma risk and are often observed in the setting of a familial melanoma syndrome. No specific presenting features of AMPs as distinct from melanoma have been clearly articulated to date.

Overall, pediatric patients should be examined much like adults, with attention to the traditional ABCD criteria, and “E” for “evolution.” Awareness by pediatricians of overrepresentation of nonwhite and amelanotic melanomas may help increase clinical suspicion. In particular, retrospective series have shown that melanomas in children are more frequently nodular, amelanotic, and thicker at presentation than in adults.²¹ Suspicious lesions should be biopsied, and whenever possible evaluated by a dermatopathologist with expertise in the evaluation of difficult melanocytic lesions.

Initial Pathologic Workup

Optimal pathologic evaluation of a clinically suspicious pigmented lesion in a child is best conducted using a team approach, emphasizing cooperation between clinician and pathologist. Key components include proper biopsy technique, communication of relevant clinical information, and correct processing of the specimen. Given the difficulty in histopathologic discrimination of benign and malignant lesions, the most desirable biopsy method is excisional biopsy. In practice, however, many lesions are sampled incompletely with partial shave or punch biopsy techniques. Formalin fixation is sufficient for all routine and specialized methods of evaluating these lesions, including fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH). Specimens should ideally be submitted to a laboratory with a board certified dermatopathologist, preferably one with experience in evaluating pediatric melanocytic lesions. Relevant clinical information for the pathology requisition includes patient age; lesion location, color, and size; and whether the biopsy includes the entire lesion. A history of congenital nevus in the area biopsied should be noted, as well as any recent changes or antecedent trauma. A clinical photograph taken before the biopsy can provide helpful documentation.^{22,23}

Essential Elements in the Pathology Report

Biopsy specimens should be embedded entirely, and at least 2 levels from each tissue block examined. The pathology report should include a microscopic description, final diagnosis, and microstaging data, as recommended for adult melanoma, even if the lesion is

diagnostically controversial. This information includes histologic subtype, Clark level, Breslow depth, dermal mitoses/mm², and the presence or absence of ulceration, regression, angiolymphatic invasion, perineural invasion, or any precursor benign lesion. The presence or absence of the lesion at biopsy edges should be noted (Figure 2).^{23,24}

Despite the difficulty in pathologic diagnosis, most pediatric melanomas show similar histologic features compared with adult melanomas, with approximately 60% of these being of the superficial spreading subtype.¹⁸ The histologic subtyping of pediatric melanoma is somewhat controversial, because a significant proportion of lesions do not conform to the standard 4 categories (superficial spreading, nodular, acral lentiginous, lentigo maligna). Although no standardized nomenclature for reporting of these other subtypes has been proposed, melanomas that resemble a Spitz nevus by virtue of cytology and/or architecture may be designated *Spitzoid melanoma*, those resembling a benign nevus may be termed *nevoid melanoma*, and those resembling cellular blue nevus may be termed *blue nevus-like melanoma*.²⁵

The pathology reporting for AMPs should mirror that of melanoma, including the histologic parameters noted earlier. The microscopic description should address the histologic features evaluated, such as circumscription, symmetry, lesion diameter, depth, pattern of junctional component, presence of epidermal hyperplasia or atrophy, Kamino bodies, sheet-like dermal growth, mitotic rate, lymphocytic infiltrate, angiolymphatic invasion, and cytologic atypia. Much histologic overlap exists between the benign nevi typically encountered in childhood, including Spitz, blue, deep penetrating, and congenital nevi, and malignant neoplasms. Table 1 presents a brief summary of the application of histologic features to diagnosis. Specialized pathology techniques have also been proposed for the evaluation of AMPs, including immunohistochemical stains and molecular/genetic analysis, detailed in the following section.

Pathologic Workup Beyond Light Microscopy

The most useful immunohistochemical markers are the melanocytic marker HMB-45, and proliferative markers such as Ki-67 and the more recently investigated phosphohistone-H3.²⁶ HMB-45 staining typically diminishes in intensity as a melanocytic proliferation “matures” with dermal depth. It is useful in evaluating Spitzoid lesions, because expression is lower-to-absent at the base of benign Spitz nevi, whereas melanomas show diffuse expression throughout the dermal component. Differential Ki-67 expression has been demonstrated in Spitz nevi (mean, 5%; standard deviation [SD], 2.46%), atypical Spitz nevi (mean, 10%, SD, 4.1%), and melanoma (mean, 37%; SD, 24.8%).²⁷ Thus while there may be some overlap in Ki-67 rates between the categories, a Ki-67 proliferation index less than 2% suggests Spitz nevus, whereas an index greater than 10% favors melanoma.²⁸ Another measure of cellular proliferation, specific for cells in active mitosis, is phosphohistone-H3. One study demonstrated lower phosphohistone-H3 immunoreactivity in Spitz nevi than in melanomas.²⁸ p16 is another potentially useful marker; expression is commonly absent in malignant melanoma, and in one study in patients younger than 18 years was absent in all 6 melanomas but present in all 16 Spitz and compound nevi.³⁰

Despite the available immunohistochemical stains, a significant number of cases defy classification through histologic means. Recently, molecular analytics taking advantage of the multiple chromosomal aberrations present in melanomas have been developed.³¹ The only commercially available test is FISH, which takes advantage of 4 color-specific probes and can be performed on formalin-fixed tissue. Although the original report showed a sensitivity of 80%, subsequent independent analyses with longer follow-up demonstrated a somewhat lower sensitivity and specificity, with tetraploidy being the most common cause of false-positive results.^{32–36} CGH, available in the research setting, is significantly more time-consuming and technically difficult.^{37–40} A subset of benign Spitz nevi demonstrate characteristic 11q abnormalities, whereas most unequivocal melanomas show numerous, often complex chromosomal aberrations.³⁵ However, the predictive value in histologically ambiguous lesions remains uncertain, and this test is not available for routine use.

Currently, no tests unequivocally determine the biologic potential of the most diagnostically difficult pediatric melanocytic proliferations.⁴¹ The authors' practice is to thoroughly evaluate all AMP lesions histopathologically, using immunochemistry as available and necessary. Molecular testing has sometimes been performed before referral; if so, it may add useful information but is not relied on for a diagnosis. If the diagnosis disagrees with the originating pathologist, a third opinion may be sought. If consensus cannot be reached concerning the benign or malignant nature of the lesion, it is signed out as "AMP," and all histologic prognostic parameters are included in the report. The biopsy results are discussed in a multidisciplinary conference and a treatment plan is formulated.

Surgical Management

Typical Spitz nevi are benign, and should be completely excised with narrow margins. Atypical Spitz tumors and other AMPs should be excised with a wider margin of normal skin, but the optimal excision margin has never been prospectively studied. Ludgate et al¹⁰ evaluated 67 patients with atypical Spitz tumors and observed a high rate of positive sentinel nodes (47%) but only one local recurrence, which occurred in the face of positive excision margins. They recommended 1-cm excision margins. The authors' experience has supported this conclusion: they treat atypical and malignant lesions in younger children (<14) with a 1-cm margin, regardless of measured thickness, and have not seen any local recurrences (Sondak VK, unpublished data, 2013).⁴² Older children and young adults are treated with excision margins based on thickness, as per the NCCN Clinical Practice Guidelines in Oncology for Melanoma (to view the most recent version of these guidelines, visit NCCN.org).^{42,43}

Staging Evaluations in Pediatric Patients With AMP

The authors recommend careful clinical evaluation of lymph node basins in all cases, and use ultrasonography, with ultrasound-guided needle aspiration cytology as necessary, to evaluate any suspicious or equivocal basins.^{44–46} Given the risks associated with ionizing radiation⁴⁷ and the extremely low likelihood of identifying distant metastatic disease in this setting, the authors do not recommend routine diagnostic imaging, such as PET/CT scans, in patients with AMP.

Whether to sample the sentinel lymph node is controversial.^{48,49} The rate of sentinel node involvement in pediatric melanoma is well established to be higher than that in adult melanoma, roughly 25% to 40%.^{50–52} Data regarding sentinel node status in AMPs are difficult to interpret, because most reports are retrospective reviews and likely have recategorized some AMPs with obvious malignancy in the nodes as melanoma. Overall, the rate of nodal positivity seems to be similar to that in pediatric melanoma.^{49,53} Similarly, eventual progression to metastatic melanoma can change an AMP diagnosis over time; thus an overly optimistic outcome has perhaps been reported in AMP retrospective series with short follow-up.⁵⁴ In at least one series, patients with AMP that was later reclassified as melanoma actually had inferior survival compared with those initially diagnosed with melanoma.⁵⁵

Sentinel lymph node biopsy (SLNB) is a well-tolerated procedure, and in the appropriate context can provide a wealth of information. In the authors' practice, SLNB is routinely used for AMPs 1 mm or thicker.⁴⁹ A negative sentinel node provides reassurance and the sense that "everything possible has been done." Even though the rate of positive sentinel nodes is high, most patients have negative nodes and would be anticipated to have an excellent prognosis.⁴⁹

A positive SLNB, however, may provide important prognostic information, including potentially establishing a diagnosis of unequivocal melanoma, and lead to a defined therapeutic plan. In the authors' experience with unequivocal pediatric melanoma, most patients who experienced recurrence had positive nodes.⁴⁸ The diagnosis of metastatic melanoma in lymph nodes from patients with AMP poses similar issues as evaluation of the primary, because nevus cells are well-known to occasionally be found in lymph nodes, termed *nodal nevi* or *nevus cell aggregates*. Benign nevus cells, including cells from Spitz or cellular blue nevi, can be present in lymph nodes draining the skin, and hence the presence of nevus cells in a node is not proof that the lesion has metastasized. The criteria for distinguishing between nodal involvement by melanoma and nodal nevi are still debated. Multiple positive nodes, expansile nodal lesions, or lesions with parenchymal deposits or necrosis are highly suggestive of melanoma. Use of p16 and Ki-67 staining has been advocated in evaluating equivocal nodes; the absence of p16 staining and/or elevated Ki-67 staining favors a diagnosis of metastatic melanoma.

Completion Lymphadenectomy in Cases of Positive Sentinel Lymph Nodes

Although unequivocally malignant findings lymph node can establish the diagnosis of melanoma in a previously diagnosed AMP, controversy remains regarding the exact prognostic significance of a microscopically positive node.⁵⁶ A positive sentinel node raises the suspicion of additional nodal disease in the remainder of the basin. Factors to consider when deciding on completion lymph node dissection include the strength of the histologic suspicion of malignancy (as indicated earlier), extent of nodal involvement, and location. Completion lymphadenectomy does have associated morbidity, especially in the inguinal and axillary regions, and this morbidity must be balanced with the anticipated benefits of the procedure. In most cases, the arguments for and against completion lymphadenectomy are similar to those for SLNB. Given the lack of definitive data and the potential consequences

of undertreating stage III melanoma, the authors routinely recommend completion lymphadenectomy in patients with AMP with a positive node, regardless of location.^{48,49,57,58} However, as for adults with unequivocal melanoma, there may be a role for nodal observation and serial ultrasonography in selected cases.⁵⁹

Role for Adjuvant Therapies in Pediatric Patients With Node-Positive AMP

In the United States, high-dose interferon alfa-2b (HDI) and pegylated interferon alfa-2b are the only approved adjuvant therapies in adults with node-positive melanoma. Despite nearly 2 decades of clinical trials, adjuvant interferon remains highly controversial in adult patients. The controversies are magnified in pediatric patients with melanoma and those with AMPs.

The ECOG 1684 trial was the first randomized study of HDI involving 287 patients with melanoma.⁶⁰ At initial publication, disease-free survival (DFS) improved and survival increased from 2.8 to 3.8 years, and both were statistically significantly improved for interferon-treated patients. Updated results showed continued statistically significant improvement in DFS but not survival.⁶¹ The authors postulated that the diminished survival benefit represented the elderly population of patients in this study, because only 75 patients were younger than 50 years. Therefore, this may not be an issue in the pediatric population. Several larger studies have confirmed the significant relapse-free survival benefit associated with interferon in adults, but the overall survival benefit has been questioned.^{62–64} A meta-analysis of 14 randomized interferon trials showed a significant improvement in both DFS and overall survival.⁶⁵ These meta-analysis data combined with case series in the pediatric population are used to justify interferon use in the pediatric melanoma population.

In adults, the side-effect profile deters many patients from receiving interferon: toxicity such as fevers, fatigue, myalgias/arthralgias, and depression limit the drug's tolerance. The small published series support that children tend to tolerate interferon therapy much better than adults. In a case series of 15 patients younger than 18 years treated with interferon, none discontinued therapy secondary to toxicity.⁶⁶ Less obvious adverse effects, such as interference with school or late central nervous system and cardiac toxicity, have been cited as reasons not to use adjuvant interferon, but have not been demonstrated in pediatric case reports.^{3,66,67} Pegylated interferon, which arguably has an improved toxicity profile, is yet another option for pediatric patients.⁶⁸ Many young patients with AMP with positive nodes (along with their parents) are extraordinarily motivated to do “everything possible” to assure a good outcome. Therefore, despite the lack of prospective data, many young patients with node-positive AMPs elect to receive adjuvant interferon.

Appropriate Posttreatment Follow-Up

Patients with AMPs should be followed up with lifelong skin examinations. In the first decade after diagnosis, these examinations should include evaluation of the regional nodes, whether or not SLNB was performed. Diagnostic imaging is not advocated for clinically or pathologically staged node-negative patients with AMP in the absence of signs or symptoms suggesting recurrent disease. Patient and family education regarding sun protection and skin self-examination also should occur regularly and repeatedly.

Conclusions

Given the many controversies and lack of prospective clinical data, AMPs warrant multidisciplinary management involving a dermatopathologist with expertise in atypical melanocytic lesions, and, unless melanoma can be completely excluded histopathologically, surgical oncologists, dermatologists, plastic surgeons, and ideally both a medical and a pediatric oncologist. A paucity of prospective and retrospective data with long enough follow-up (>10 years) exists, although national registries may eventually provide additional data to help make these difficult clinical decisions easier. Although clinical trials are ideal, they are likely to focus on cases of unequivocal melanoma.

The authors' philosophy is that the approach to treating AMPs requires excellent communication and sustained vigilance, from biopsy to pathologic interpretation, to surgical staging, and finally, to consideration of systemic therapy. Careful consideration is given to SLNB, and patients with sentinel nodes containing neoplastic cells are considered for completion lymph node dissection and adjuvant interferon, recognizing the important benefits of maximizing available information and providing reassurance that everything possible has been done. Ultimately, this approach should minimize, but cannot entirely eliminate, the possibility of patients with AMPs later being diagnosed with advanced-stage melanoma.

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Figure 1.

(A) Typical Spitz nevus from 10-year-old patient. Note small size, symmetry, and maturation of dermal component. Hematoxylin-eosin, 10x. (B) Atypical Spitz nevus from 18-year-old patient. Compared with Figure 1A, the lesion is markedly more cellular, with epidermal effacement and sheet-like dermal growth of monomorphous melanocytes that do not demonstrate maturation. (C) Spitzoid melanoma from 17-year-old patient. Although resembling a Spitz nevus by virtue of epidermal hyperplasia and epithelioid cell component, there is marked atypia and sheet-like growth of dermal component, with severe pleomorphism in the deeper portions of the lesion. (D) Sentinel node from patient whose lesion is shown in Figure 1C. There is a subcapsular nest of atypical melanocytes similar to those found in the primary tumor. The subcapsular location distinguishes this from a nodal nevus.

Table 1

Overview of Salient Features of Melanocytic Proliferations

	Spitz Tumor	Atypical Spitz Tumor	Spitzoid Melanoma	Deep Penetrating Nevus	Atypical Cellular Blue Nevus
Asymmetry: low-power growth	Symmetric, wedge-shaped	Usually asymmetric	Asymmetric	Symmetric, wedge-shaped	Lobular, well-circumscribed
Border	Sharp lateral circumscription	Poor	Poor	Present, if junctional component	N/A
Cell type	Spindle and epithelioid	Mostly spindled	Heterogenous	Small ovoid melanocytes	Dendritic and oval melanocytes
Diameter	<1 cm	1 cm	1 cm	<1 cm	>1 cm
Dermal growth	Nested	Sheet-like	Sheet-like	Nested, periadnexal, and perivascular	Periadnexal, perineural, perivascular
Mitotic rate	<2/mm ²	2–6/mm ²	2/mm ² , atypical	<2/mm ²	>2/mm ²
Maturation with descent	Always present	May be absent	Absent	Absent	Absent
Pagetoid spread	Minimal	Present	Abundant	Absent	N/A

Abbreviation: N/A, not applicable. Features can only be assessed in lesion with junctional component.