Spitzoid melanoma of childhood: a case series and review

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Practice points
• Atypical Spitz tumors (AST) and Spitzoid melanomas (SM) are biologically distinct from adult type melanomas (MM).
• AST and SM are usually treated as per current MM management guidelines.
• Existing data suggest that adjuvant therapy may not be necessary in fully resected nonmetastatic sentinel lymph node-positive (SLB+) SM/AST and that these patients could be observed as they are unlikely to recur.
• A great degree of variability exists in the management of these tumors amongst pediatric oncologists.
• Further molecular studies are needed to understand the unique biological behavior of AST/SM. These studies may ultimately lead to important insights into transformation of benign nevi into melanomas and identify new therapeutic targets in advanced melanoma.

SUMMARY Spitzoid melanomas (SM) and atypical Spitz tumors (AST) are rare pediatric neoplasms. We performed a retrospective, single-institution review and report our institutional experience. We identified 10 patients (median age: 12.5 years). A sentinel node biopsy (SNB) was performed in 8/10 (80%) patients, and interestingly 7/8 (87.5%) were found to be positive for malignant cells. A complete regional lymphadenectomy was performed in all SNB-positive patients, but only 2/8 (25%) were found to have additional lymph node spread. Adjuvant therapy was administered in 5/8 SLNB-positive and 2/2 (100%) regional LN-positive cases. All patients had excellent long-term outcomes (100% survival). This report highlights the excellent outcomes associated with SNB + pediatric SM and AST.

Spitzoid melanoma (SM) and atypical Spitz tumors (AST) are rare neoplasms that affect children. SM and AST often pose a diagnostic challenge, as these lesions are often hard to distinguish from adult type malignant melanoma (MM) based on pathologic criteria [1,2]. The optimal management of SM/AST remains controversial [3]. Management usually consists of surgical removal of large, rapidly changing lesions with atypical dermoscopic or histological features [4,5]. Complete lymphadenectomy is usually performed in patients with sentinel lymph node positivity [5–8].

This report summarizes our institutional experience in treating these rare pediatric tumors.

Methods

We retrospectively collected clinical data from the melanoma database in patients ≤21 years of age diagnosed with SM/AST from 1980–2014, at Riley Hospital for Children, Indianapolis, after approval by our Institutional review Board. Every year, approximately two to four pediatric patients with newly diagnosed melanoma are diagnosed and treated at Riley Hospital.

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The tumors were classified as AST or SM if they displayed all or some of the following features: asymmetry, epidermal effacement, high cellular density, cytological atypia, high nuclear/cytoplasmic ration, mitotic rate >2/mm^2 (AST and SM) and a high degree of pleomorphism (SM) [9,10]. In all patients, a second opinion from an external expert pathologist was obtained, to confirm the diagnosis. However, some of the cases were diagnosed and managed in the 1980s and 1990s, and the pathological criteria at that time might have been less defined than the current criteria. Thus a limitation of this study is observer bias.

Results

Ten cases of SM/AST were diagnosed and managed at our institution from 1980–2014. The histopathological features and patient demographics, treatment and outcomes are summarized in Tables 1 & 2, respectively.

The median age of the ten patients was 12.5 years. The median follow-up was for 34 months. All patients were alive, with no local or distant disease recurrence. Six out of ten patients had a complete and wide excision of the primary lesion with negative margins. Four patients (patient # 2, 3, 5 and 6) underwent a re-excision with negative margins. A SLB was performed for all stage III lesion (8/10 = 80%) and was found to positive (SLB+) for atypical malignant cells in 7/8 (87.5%, 6/8 of these had isolated tumor cells and 1/8 [patient #6] had extensive involvement) samples. All SLB+ patients underwent a regional lymph node dissection (LND) but only 2/8 (25%) of the dissected lymph nodes were positive (LND+) for malignant cells.

Two patients (# 2 and 5), who were SLB+/LND-, were observed and received no further therapy. Three patients (patient numbers 3, 4 and 8, SLB+, LND-) received adjuvant immunotherapy (interferon [IFN]) (Table 2). Both patients with regional nodal disease (patient numbers 6 and 10) received IFN and local radiotherapy (RT) or IFN only respectively (Table 2). Patient numbers 1 and 7 did not undergo a SLB and were presumed to be stage II.

Abnormal and varied cytogenetics were documented in four patients (patient # 2, 3, 5 and 7). Melanoma specific FISH probes, *BRAF* and *RAS* mutations were not tested in these patients. Interestingly, the two SLB+ patients, who were observed, were found to have atypical cytogenetic findings of 6q-, total loss of chromosome 9 and 10, and 1q-, 2p-, loss of chromosome 9 and 19, respectively, remained relapse free 17 months and 50 months postresection.

Discussion

SM/AST are rare pediatric tumors that are a distinct clinicopathologic entity, first described by Spitz in 1948. Consistent with our results, a higher incidence of sentinel node positivity (SLB+) has been reported in SM/AST compared with malignant melanoma [6–7,11]. The higher incidence of SLB+ is usually not associated with either extensive nodal involvement or distant metastasis, especially in prepubescent children (only 25% in our case series) and importantly doesn't usually translate into inferior outcomes [7,12–14].

The increased propensity to metastasize to local lymph nodes but not distant sites could be explained by a vigorous immune reaction, better microfiltration, natural involution of lymph

Patient	Histology	Breslow thickness	Clark level	Ulcer	V/L invasion	Mitosis/ mm^2	Margins	Associated nevus	Cytogenetics
1	SM	NA	NA	NA	NA	NA	Negative	No	NA
2	SM	Intermediate (1–3.99 mm)	IV	No	No	3	Positive	No	6q-, 9-, 10-
3	SM	Intermediate	IV	No	NA	12	Positive	No	1q-, 2p-, 2q-, 9- (total loss), 19-
4	SM	Intermediate	NA	NA	NA	NA	Negative	Yes	3q-, 6p-
5	SM	Intermediate	NA	No	NA	NA	Positive	No	2p-, 18-, 16q-, 12q-
6	SM	Intermediate	III	No	No	NA	Negative	Yes	NA
7	SM	Higher risk (>4 mm)	IV	Yes	No	NA	Negative	NA	11p+, 15+, 18+, 22+, 3q-, 13q-
8	AST	Intermediate	IV	No	NA	NA	Negative	Yes	NA
9	AST	NA	NA	No	NA	NA	NA	Yes	NA
10	AST	Higher risk	NA	No	NA	NA	NA	Yes	NA

Table 1. Histopathologic features.

AST: Atypical Spitz tumors; SM: Spitzoid melanoma; NA: Information not available.

Patient	Age (years)	Sex	Site	Wide excision	Sentinel LN	Regional LND	Stage	Adjuvant therapy	Status	Follow-up (RFS)
Table 2. Patient demographics and clinical follow-up.										
1	14	Male	Extremity	Yes	No	No	II	No	Alive	24
2	6	Female	Extremity	Yes†	Yes(+)	Yes (-)	IIIA	No	Alive	17
3	16	Female	Extremity	Yes†	Yes (+)	Yes (-)	IIIA	IFN × 2 yrs	Alive	27
4	10	Male	Extremity	Yes	Yes (+)	Yes (-)	IIIA	IFN × 1 year	Alive	34
5	2	Female	Head/neck	Yes†	Yes (+)	Yes (-)	IIIC	No	Alive	50
6	13	Male	Head/neck	Yes†	Yes (+)	Yes (+)‡	IIIC	IFN × 1 year, Local RT	Alive	34
7	4	Female	Head/neck	Yes	No	No	IIC	No	Alive	84
8	14	Male	Head/neck	Yes	Yes (+)	Yes (-)	III	IFN × 48 weeks	Alive	12
9	15	Male	Head/neck	Yes	Yes (-)	Yes (-)	III	No	Alive	84
10	12	Male	Head/neck	Yes	Yes (+)	Yes (+)	III	IFN	Alive	60

†Patient 2, 3, 5 and 6 underwent a re-excision after partial resection.
‡Patient 6 had multiple regional LN that were positive and had extra capsular local spread.
LN: Lymph node; LND: Lymph node dissection; RFS: Relapse-free survival; RT: Radiotherapy.

nodes in the pediatric population [15]. One could also hypothesize that the malignant cells that are identified in the lymph nodes are nodal melanophages that have been over interpreted as aggressive melanoma cells [16].

Whether or not SM/AST represent a continuum between benign nevi and aggressive adult type malignant melanoma remains a mystery. Majority of malignant melanomas demonstrate chromosomal aberrations and gene amplifications [17,18], and loss of replicative senescence by telomerase overexpression [19] and angiotropism [20]. While the majority of conventional pediatric melanomas demonstrate a bigger array of chromosomal copy number aberrations, they may also demonstrate 6p25, 8q24 and 11q13 gains, deletions of 6q23 and 9p21, like their Spitzoid counterparts [21–25].

Benign Nevi such as blue or congenital nevi usually do not exhibit similar cytogenetic abnormalities or telomerase overexpression but may exhibit angiotropism [26–28].

Using comparative genomic hybridization (CGH) and FISH, gains in 6p25 or 11q13 and homozygous deletions in 9p21 have been identified in SM/AST and were found to be associated with a more aggressive clinical behavior and higher propensity towards metastatic spread beyond the sentinel lymph node [22,29].

Based on this observations, one could speculate that unique chromosomal aberrations and dysregulation of the telomere checkpoint may play a role in determining the phenotype of a SM/AST [24–25,30–32].

SM also have a unique spectral signature further suggesting that these neoplasms are biologically unique and differ in pathogenesis from MM, especially in the prepubertal pediatric age group [18,33]. A small subset of Spitz nevi demonstrate an isolated gain of chromosome 11p and *HRAS* mutations [32,34], a finding not seen in adult type melanoma. *HRAS* mutations seem to confer a benign clinical behavior. Unlike conventional melanomas, *NRAS* mutations are rare in Spitzoid lesions [21,35–36]. More recent studies have demonstrated the presence of additional kinase fusions (*ROS1*, *NTRK1*, *ALK* and *RET* oncogenes) in adult Spitzoid neoplasms [30], but little is known of the precise role of these oncogenes in the transformation of Spitz nevi into AST and SM.

Activating mutations of BRAF kinase are common in MM [37]. However, *BRAF* mutations have also been found in benign nevi, suggesting that *BRAF* mutation is an early mutagenic event that by itself may not confer malignant potential [35,36]. The heterogeneity of *BRAF* mutations while documented in adult type melanoma and other tumor types, have not been elucidated in pediatric AST or SMs but warrants further investigation [2,21]. Like their adult counterparts, the heterogeneity of *BRAF* mutations, may ultimately dictate clinical response to BRAF inhibitors in this patient population, and may ultimately provide the foundation for the use of kinase inhibitors for the treatment of refractory SM and ASTs [2,21].

Another biological feature of aggressive MM is the ability to evade effective immune response possibly by inhibiting T-cell activation [38–40]. The PD-1 receptor has been shown to attenuate activated T cells to mount an immune response

towards melanoma cells [41–43]. Melanoma cells produce the ligand (PD-L1) which binds PD-1 on the T-cell surface. Recent trials have demonstrated that Ipilimumab, a monoclonal antibody to CTLA-4 receptor and PD-1 is efficacious in advanced melanoma [43].

One could speculate that one of the reasons, majority of ASTs and SMs may not be able to evade host immune response and tend to be limited to local spread, is that they do note attenuate activated T cells via the PD-1 pathway. It is plausible that the ASTs or SMs that are fatal and metastasize may have effectively evaded host response in a similar manner to MM.

Conclusion

A great degree of variability still exists in the management of AST and SM among pediatric oncologists especially regarding the use of adjuvant therapy in these patients.

In the past, metastatic or aggressive AST or SM have been treated as per current MM management guidelines. However, as our case series demonstrates, clinicians should elect to observe fully resected nonmetastatic SLB+ SM/AST, based on the notion that these are biologically a different entity than adult type malignant melanoma. While postpubescent state, presence of homozygous 9p21 deletion or a high number of chromosomal aberrations may confer a higher risk of advanced local-regional disease, it does not necessarily translate into inferior outcomes [13,44]. Our experience further supports the notion that the aggressive clinical approach used in adult melanoma may not be applicable to sentinel node-positive SM/AST, as the relapse or recurrence rate is low with or without adjuvant therapy.

Future perspective

AST and SM are clinically and biologically different from MM. Based on our observations and emerging clinical data these rare pediatric neoplasms may have been overtreated in the past, especially if the treating physician followed current MM management guidelines. The majority of these lesions can simply be excised or re-excised, followed by careful physical, radiological or echotomographic monitoring of the regional nodes.

Little is known about what determines the unique clinical behavior of pediatric AST and SMs, and why these tumors are associated with better outcome even if they metastasize locally. Further molecular studies are needed to understand the unique biological behavior of these rare pediatric tumors. These studies may ultimately lead to important insights into transformation of benign nevi into melanomas and identify new therapeutic targets in advanced melanoma.

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