Adjuvant immune checkpoint inhibitor therapy may benefit pediatric patients with stage III melanoma and sentinel lymph node positivity: a Case Series

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Abstract

Background: Melanoma is the most common skin cancer in children. While the current literature establishes treatment protocols for adult-type melanoma, very few pediatric-specific studies exist, and children are often excluded from melanoma clinical trials [2]. **Case Report:** We report a case series of 23 consecutive pediatric patients diagnosed with melanoma at the University of Rochester Medical Center between 1/1/2011 and 1/1/2022. 2/23 (8.7%) patients had recurrence of their malignancy after therapy while 21/23 (91.3%) remained without disease progression; 1 patient died from unknown cause, but the rest are alive and currently without disease. All patients whose initial therapy included nivolumab in addition to wide local excision did not have recurrence or progression of their disease. **Conclusions:** This case series highlights trends in the presentation, treatment, and outcomes of pediatric melanoma; however, additional multi-center studies are needed to establish the clinical utility of such features in pediatric melanoma.

Introduction:

Pediatric melanoma is the most common skin cancer in children. However, it is very rare with only 300-500 new reported cases annually in the United States[1]. While the current literature establishes treatment protocols for adult type melanoma, very few pediatric-specific studies exist, and children are often excluded from melanoma clinical trials[2]. There is a need to identify therapeutic strategies for pediatric melanoma as some subtypes, including atypical Spitz tumors and Spitzoid melanomas, are biologically distinct from adult-type melanomas[3]. Features that have proven to be valuable in predicting a positive response to targeted therapies and/or immunotherapies in adults with melanoma include ulceration, Breslow thickness, cytogenetic abnormalities, and staging[4]. However, more research is needed to further elucidate how these clinical and histopathologic features influence pediatric melanoma outcomes.

We report our experience with children under 21 years of age diagnosed with and subsequently treated for melanoma.

Case Series:

All patients diagnosed with melanoma before 21 years of age and treated at the University of Rochester Medical Center between January 2011 and December 2022 were included in this retrospective, Institutional Review Board (IRB) approved, case series. Patient demographic and clinical information was assessed and collected including assigned sex at birth, mean age at diagnosis, diagnosis, stage of melanoma at diagnosis, initial therapy, response, family history, and clinical features of melanoma.

Patients Characteristics

Twenty-three patients (median age: 13 years, age range: 2-20 years) were diagnosed with melanoma with the following histopathologic subtypes: Spitzoid melanoma (5), melanoma in situ (3), superficial spreading melanoma (2), nevoid melanoma (1), nodular melanoma (1), severely atypical spindle cell melanocytic tumor (1), and pigmented epithelioid melanocytoma (1). In 9 cases, a conventional histopathologic subtype was not reported. Melanoma staging ranged from Stage 0 to Stage IIIC. Tumor genetic testing was performed on 10 patients. All patients received wide local excision (WLE) as initial treatment at the University of Rochester Medical Center between 2011 and 2022 (Table 1). Breslow thickness was reported in 17/23 patients and ranged from 0.5 mm to 7.8 mm. The melanomas were found at the following locations foot (2), leg (4), arm (2), hand (3), shoulder (2), head (3), back (4), axilla (1), flank (1) and buttock (1).

Six patients (26%) self-reported a history of sunburns that was documented in their electronic medical record and 5 patients (21.7%) reported a family history of melanoma (Table 2). Twelve patients (52%) presented for evaluation due to changes in their pre-existing "moles" (melanocytic nevi) with 8 reporting increasing size, 5 reporting changes in color and 2 reporting bleeding. Melanoma arose de novo in 9 patients (39.1%), from congenital melanocytic nevi (CMN) in 3 patients (13%), and from acquired melanocytic nevi in 2 patients (8.7%). The origin of melanomas in 9 (39.1%) patients was not mentioned or was unable to be categorized based on histopathology and patient presentation.

Genetic Testing

Genetic testing was performed on the excised tissue in 43.5% (10/23) of cases. *BRAF* tissue testing was performed in 5 patients and was negative in all (5/5). In 1 patient with Spitzoid melanoma, immunohistochemistry stains showed that the large atypical cells were diffusely and strongly positive for *SOX-10* and *S-100* and negative for p 16, *CD34* , desmin and *SALL-with*retention of BAP1 expression throughout the tumor. Another 2 patients with Spitzoid melanoma also had retained *BAP1* . One patient with melanoma in situ underwent a chromosomal microarray, p 53 sequencing and deletion/duplication testing that were all normal.*BRCA2* mutation was negative for a patient with melanoma of unspecified subtype. Two patients were tested with the Castle diagnostics gene expression profile assay; one was classified as stage 2B with the highest risk of recurrence and/or metastasis within the next 5 years while the other patient was classified as stage 2A with an increased risk of recurrence or metastasis within the next 5 years. The patient with the stage 2A classification was also tested via the Invitae Multi-Cancer Panel with resulting variants of unknown significance (VUS) in *AIP* , *CASR* , and *MSH3* and no mutations in*BRAF* .

Initial Treatment

All patients received WLE in accordance with the National Comprehensive Cancer Network (NCCN) surgical management of melanoma guidelines. Of the nineteen patients who underwent a sentinel lymph node biopsy (SLNB) at the time of WLE, 11 had a positive SLN (57.9%). Of these 19 patients, 6 received nivolumab, 1 received interferon alpha-2b, and 1 received tremelimumab within 90 days of the WLE. Out of the three patients with ulceration, two received nivolumab. Eighteen patients were considered in complete remission (CR) following their initial treatment. Two patients had recurrence of their melanoma (at 10 and 19 months from WLE) and 2 other patients were still undergoing initial nivolumab treatment at the time of the writing of this article. The patients (n=6) whose initial therapy included nivolumab in addition to WLE did not show recurrence or progression of their disease. Out of the 6 patients who received nivolumab therapy, 4 had no adverse events (66.7%), 1 had a grade 3 lichenoid drug eruption (leading to treatment discontinuation) and 1 had peripheral eosinophilia (prompting treatment withholding for 1 month).

Recurrence

Melanoma recurred in two patients following initial therapy with WLE, one at Stage III and one at Stage 0. Both had a family history of melanoma. One patient was diagnosed with melanoma in situ on the left thumb. Biopsy showed positive margins and the initial SLNB was positive. Upon recurrence, the patient underwent repeat excision with positive margins and SLNB that was negative. The other patient diagnosed

at Stage IIIc had a history of sunburns and presented for a newly growing "mole" on the right preauricular cheek. Skin biopsy revealed a non-ulcerated superficial spreading melanoma with Breslow thickness of 2 mm and positive margins. SLNB was positive. *BRAF* mutation was negative. Treatment at recurrence included radiation, complete neck dissection (levels I-V), parotidectomy, as well as ipilimumab, nivolumab, and pembrolizumab. After the last dose of nivolumab, the patient experienced symptoms of checkpoint colitis, however colonoscopy was negative, and the patient's condition subsequently improved with steroids.

Patient Outcomes

With a mean time from diagnosis to initiation of treatment of 31.8 days (range: 0-70 days), 21/23 (91.3%) patients remained alive and disease-free as of February 14, 2023, at a median of 3.39 years (range 0.11 – 11.8 years) of follow up (Figure 1). Two patients had recurrence, both remain alive and currently disease-free with salvage therapies. No patients died from melanoma. Due to the small size and nature of this study, we cannot claim significant survival differences between patient cohorts. Nevertheless, patients who received nivolumab (n=6) at the time of initial treatment did not have recurrence or progression of their melanoma. Of the 9 patients diagnosed at Stage III with at least 1 positive SLN, 6 received nivolumab and did not have recurrence/progression, 1 did not receive nivolumab and had recurrence, and 2 did not have recurrence/progression although 1 of them received interferon as part of the initial treatment (Table 2).

Discussion:

We report a case series of pediatric melanoma adding to the growing data on the diagnosis and management of this rare malignancy. Sixty-five percent of the patients in this cohort were diagnosed with melanoma in adolescence (age [?] 11 years). Moreover, both patients that progressed were older than 11 years old at diagnosis, supporting the existing literature stating that adolescent melanoma has a more aggressive disease course compared to pre-pubertal melanoma[5].

Outcomes were favorable, with event-free and overall survival of 91% and 100%, respectively. Our data suggest that including nivolumab in the initial treatment of melanomas diagnosed at Stage III may help avoid recurrence or progression of melanoma. Four out of the 9 patients diagnosed at Stage III did have Spitzoid melanoma and 3 of them were diagnosed in younger childhood (age $<$ 11 years). Multiple other studies similarly found that Spitzoid melanomas occur more commonly in pre-pubertal age [5-8]. It is generally thought that patients with Spitzoid melanoma have higher rates of positive SLN despite an excellent overall prognosis[8]. Additionally, we observed no progression or recurrence of melanoma in the remaining 3 patients diagnosed at Stage III with either melanoma of unspecified subtype (n=2) or severely atypical spindle cell melanocytic tumor (n=1). We also observed that among the 19 patients who had an SLNB, prepubertal patients ($<$ 10 years of age) had a lower percentage of SLN positivity (57%) when compared to adolescent patients (75%). This differs from the findings by Moore-Olufemi *et al.,*Pol-Rodriquez *et al.* and El Sharouni *et al.* , but our small sample size is much smaller[7,9,10].

Nivolumab therapy was initiated in 7 patients, and was well tolerated in most (5/7, 71%). Patients experienced either no adverse events (n=3) or Grade 1 or 2 toxicities including mild dermatitis (n=1) and chills (n=1) that improved with steroid administration. Nivolumab treatment was discontinued in one patient who had a grade 3 lichenoid drug eruption and withheld in 1 patient who developed hyper-eosinophilia. Although the safety of nivolumab has not been extensively studied in the pediatric population, a study by Davis *et al.* showed that nivolumab is safe and well-tolerated in children and young adults[11]. A small case series (n=10) that included 5 patients with skin melanoma further supports the safety and efficacy of nivolumab in pediatric patients. Complete remission was achieved in 3 patients with melanoma (60%)[1]. In our cohort, we observed complete remission in all the patients (100%) treated with nivolumab.

Melanoma in pediatric patients can present differently than in adults: 39% of the pediatric population in this study were diagnosed with Stage III melanoma which aligns with previous studies suggesting children are diagnosed at later stages than adults[8.] This is most likely due to the relative rarity of melanoma and paucity of research on the clinical and histopathological features indicative of melanoma in the pediatric population. Our case series also suggests that ulceration is less of an adverse prognostic finding in children

than it is in adults as only 3 patients had ulcerated lesions. Of those 3 patients, 2 received nivolumab and all three achieved CR after initial therapy. Current literature supports these findings with similar reports of lower frequencies of ulceration histologically[12].

While Sharouni *et al* ., observed that a Breslow thickness > 4 mm predicted worse survival, in our case series, none of the patients with a reported Breslow thickness of > 4 mm had recurrence or progression[7]. Of the 2 patients that had a recurrence, 1 was diagnosed with a Breslow thickness of 2 mm, while the other did not have a reported Breslow thickness. Sharouni*et al* ., also noted that all 3 children who recurred had melanomas located on the head or neck. Only 3 of our patients were diagnosed with head/neck melanomas and of those 1 (33.3%) developed a recurrence.

Another factor influencing the prognosis of pediatric melanoma is its genomic subtype. Non-spitzoid melanomas typically have evidence of UV exposure with a large number of C>T transitions at dipyrimidine sites, *BRAF* and *TERT* promoter mutations and inactivation of *PTEN* [13]. Of the 4 patients diagnosed with a non-spitzoid type melanoma who underwent genetic testing, none had these mutations. Instead, 2 patients had negative*BRAF* mutations, 1 only underwent a chromosomal microarray and*p53* sequencing and deletion/duplication testing and 1 underwent a diagnostics gene expression profile that did not include *BRAF* . These findings are limited by the size of our case series. Additionally, most of our patients with non-spitzoid melanoma did not undergo genetic testing (12/18, 67%). All patients diagnosed with melanoma should undergo genetic testing as taking a combined genomic and clinicopathologic approach has been shown to optimize diagnosis and treatment[13]. Pappo *et al.* , demonstrated that the genomic differences between spitzoid melanoma, conventional melanoma and melanoma arising from a congenital nevus can influence treatment and thus clinical outcomes[13].

Lastly, our findings differ from existing literature suggesting that the majority of melanomas arise de novo rather than in conjunction with a pre-existing nevus[5,14]. While there is no universally agreed upon histological definition of nevus-associated melanoma, pathology-based studies have found that 20% to 30% of melanomas contain nevus cells in histologic continuity with melanoma[15]**.** In our study, only two of the melanomas had evidence of normal nested melanocytes to support an origin in an acquired nevus. This is similar to adult melanoma where research indicates most melanomas develop as new growths and supports the findings that the lifetime risk for an individual nevus to transform into melanoma is quite low, particularly in younger individuals[6]. However, while nevus-associated melanomas are not common, they should not be considered incidental phenomena as incidence is shown to be higher than what would be expected by chance alone[5].

Conclusion

Pediatric melanoma appears to present at more advanced stages in comparison to adult melanoma, though pediatric patients have a relatively outstanding outcome in our cohort. Incorporating nivolumab into the initial treatment of melanoma in the pediatric population may be associated with decreased progression and recurrence in children diagnosed at stage III with at least one positive SLN. While more extensive research into its toxicity and its application in pediatric melanoma is needed, nivolumab appears safe and well-tolerated in our small pediatric cohort. Our data support that histological ulceration does not seem to be an indicator of poor prognosis for melanoma in the pediatric population and that melanoma in children is more likely to arise de novo rather than a pre-existing melanocytic nevus. These differences between melanoma in children and adults may explain why children are being diagnosed at more advanced stages. Therefore, more research outside of the established clinical and histopathologic features used for the adult population is needed.

TABLE 1 . Patient demographic data and melanoma types.

Characteristic	Characteristic	All patients with melanoma (N=23)	Patients without Staging (n=2)	Patients with Stage 0 (n=3)	Patients with Stage I (n=5)	Patients with Stage II (n=4)	Patients with Stage III (n=9)
Age, mean	**Age, mean**	12.8	8.5	11.5	15.6	14.5	11.4
Sex, n (%)	Female Male	12 (52.2) 11 (47.8)	1 (50) 1 (50)	1 (50) 1 (50)	5 (83.3) 1(16.7)	3 (75) 1 (25)	2 (22.2) 7 (77.8)
Diagnosis, type n (%)	Melanoma, undefined Spitzoid Melanoma in situ Superficial spreading Nevoid Nodular Severely atypical spindle cell Pigmented epithelioid melanocytoma	9 (39.1) 5 (21.7) 3 (13) 2 (8.7) 1 (4.3) 1 (4.3) 1 (4.3) 1 (4.3)	1 (50) 1 (50)	0 (0) 0 (0) 3 (100) 0 (0) 0 (0) 0 (0) 0 (0)	4 (66.7) 0 (0) 0 (0) 1 (16.7) 0 (0) 0 (0) 0 (0) 0 (0)	1 (25) 1 (25) 0 (0) 0 (0) 1 (25) 1 (25) 0 (0) 0 (0)	3 (33.3) 4 (44.4) 0 (0) 1 (11.1) 0 (0) 0 (0) 1 (11.1) 0 (0)

TABLE 2. Patient melanoma characteristics and outcomes.

Characteristic		All patients with melanoma (n=23)	Patient without Staging (n=2)	Patients with Stage 0 (n=3)	Patients with Stage I (n=5)	Patients with Stage II (n=4)	Patients with Stage III (n=9)
Initial Therapy (n=23)	WLE & SLNB WLE Immunotherapy	18 (78.3) 5 (21.7) 8 (34.8)	2 (100)	1 (50) 1 (50)	3 (50) 3 (50)	4 (100)	9 (100) 8 (88.9)
Response (n=23)	No progression/recurrence Progression Recurrence	21 (91.3) 2 (8.7)		2 (100) 1 (50)	6 (100)	4 (100)	8 (88.9) 1 (11.1)
Margins (n=23)	Positive Negative	9 (39.1) 14 (56.5)	2 (100)	1 (50) 1 (50)	2 (33.3) 4 (66.7)	2 (50) 2 (50)	4 (44.4) 5 (55.6)
Ulceration (n=21)	Yes No	3 (13) 18 (78)	1 (50)	2 (100)	6 (100)	1 (25) 3 (75)	2 (22.2) 6 (66.7)
Presence of other melanocytic nevi (n=22)	Yes No	18 (81.8) 4 (18.2)	2 (100)	1 (50)	4 (66.7) 2 (33.3)	4 (100)	7 (77.8) 2 (22.2)

Characteristic		All patients with melanoma (n=23)	Patient without Staging (n=2)	Patients with Stage 0 (n=3)	Patients with Stage I (n=5)	Patients with Stage II (n=4)	Patients with Stage III (n=9)
Therapy at progression or recurrence*	Radiation Surgery Immunotherapy	1 (50) 2 (100) 2 (100)					1 (50) 2 (100) 2 (100)
History of sunburns (n=23)	Yes No	6 (26.1) 17 (73.9)	1 (50) 1 (50)	3 (100)	1 (20) 4 (80)	2 (50) 2 (50)	2 (22.2) 7 (77.8)
Family history of melanoma (n=23)	Yes No	6 (26.1) 17 (73.9)	2 (100)	1 (50) 1 (50)	2 (33.3) 4 (66.7)	1 (25) 3 (75)	2 (22.2) 7 (77.8)
Family history of dysplastic nevi syndrome (n=23)	Yes No	1 (4.3) 22 (95.7)	2 (100)	2 (100)	1 (16.7) 5 (83.3)	4 (100)	9 (100)
Positive SLNB (n = 19)	Yes No	11 (47.8) 8 (52.2)	2 (100)	1 (50)	1 (16.7) 2 (40)	4 (100)	9 (100)

*percentage of those who recurred only, ˆtreatment ongoing

TABLE 3. Patients treated with nivolumab presentation and outcomes.

Patient	Sex	Age at Diagnosis	Histologic Subtype	Treatment Received	Adverse Effects of Treatment	Genetic Findings	Clinical Response	Follow-up from Diagnosis (years)
A	M	9	Spitzoid	WLE, nivolumab	Chills	*BAP1* retained	CR	0.12
B	M	12	Spitzoid	WLE, nivolumab	Grade 3 lichenoid eruption	*BRAF* neg, VUS in *POLE*	CR	3.01

Patient	Sex	Age at Diagnosis	Histologic Subtype	Treatment Received	Adverse Effects of Treatment	Genetic Findings	Clinical Response	Follow-up from Diagnosis (years)
C	F	10	Spitzoid	WLE, nivolumab	Mild dermatitis that improved with steroids	*BAP1* retained, positive for *SOX-10* and *S-100*, neg for p16, CD34, desmin and *SALL-4,* Ki67 20-50%	CR	2.05
D	M	8	Severely atypical spindle cell melanocytic tumor	WLE, nivolumab	No autoimmune effects	Not tested	CR	0.98
E	M	9	Spitzoid	WLE, nivolumab, left neck dissection, radiation	Hypothyroidism, hypereosinophilia	Negative Invitae Multi-Cancer Panel	CR	3.40
F	M	13	Unspecified	WLE, Nivolumab, complete neck dissection levels I-IV, radiation	No autoimmune effects	Class 2B Castle Diagnostics Gene Expression Profile	CR	1.24

Patient	Sex	Age at Diagnosis	Histologic Subtype	Treatment Received	Adverse Effects of Treatment	Genetic Findings	Clinical Response	Follow-up from Diagnosis (years)
G	M	20	Superficial spreading	WLE, right neck dissection, nivolumab,superficial parotidectomy at progression	Colitis with negative colonoscopy that improved with steroids	Neg for *BRAF*, *KIT*, *IDH2*, *MAP2K1*, *PDGFRA*, *EGFR*, *MET*, *PIK3CA*, *IDH1*, *KRAS*, *NRAS*, VUS in *AIP* and *EGF*	Initially progressed Now CR	2.10

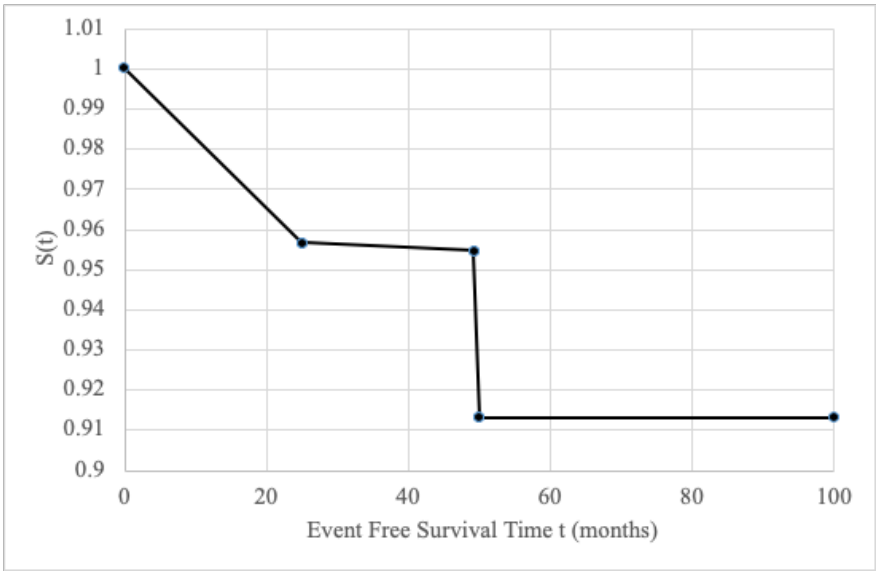

FIGURE 1. Event free survival Kapplan Meier curve.

Patients/Guardian's Consent

Not applicable

Ethical Clearance

Not applicable

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Declaration of Competing Interest

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