Pediatric melanoma and aggressive Spitz tumors: a retrospective diagnostic, exposure and outcome analysis

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Background: The diagnosis and management of pediatric melanomas is challenging given the presence of both melanomas and histologically aggressive Spitz tumors of undetermined biological significance (S-UBS) in this age group. Study objectives were to examine: factors leading to diagnostic delays, therapy side effects and patient outcomes in these diagnostic groups.

Methods: A retrospective case review was performed using The University of Michigan's pediatric oncology database over a 13-year timespan. Patients referred to our clinic for consideration of interferon therapy due to a diagnosis of a stage III melanoma or aggressive appearing S-UBS with significant lymph node involvement were included.

Results: We found two major causes of diagnosis delay: patients with amelanotic lesions misdiagnosed as having a wart and cases reviewed by non-expert pathologists upfront. The side effects from interferon therapy requiring dose adjustments included neutropenia, thrombocytopenia and mood disturbances. There was wide variability in surveillance scan utilization, therefore leading to variability in patient radiation exposure. Unlike melanoma patients, none of the S-UBS patients experienced disease progression or death.

Conclusions: This study highlights the challenges with the initial clinical diagnosis and pathological sub-categorization of the pediatric S-UBS/melanoma spectrum of skin lesions and emphasizes the role of expert pathology review upfront. Further, education at the primary care level could improve accurate and timely diagnoses. Earlier diagnosis could spare patients from more extensive interventions, metastatic spread or adverse outcomes in this patient population. This study is limited due to its retrospective, single-institution perspective.

Keywords: Melanoma; Spitz tumor; interferon

Introduction

Melanoma remains a rare but serious pediatric disease, with incidence ranging from 0.3–2% of all total melanomas diagnosed depending on the study and the precise patient populations examined (prepubertal versus pubertal) (1,2). True pediatric melanomas and melanocytic lesions such as Spitz tumors of undetermined biological significance (S-UBS) are rare and lead to a number of clinical challenges in the diagnosis and treatment of such lesions (3-8). While

"classic" adult melanomas follow the standard "ABCDE" (asymmetry, irregular borders, color variety, large diameter, and evolving), pediatric melanomas can often be colorless (9), lending to potential challenges in initial lesion identification in the primary care setting.

While it has been suspected that S-UBS behave differently/less malignantly than true melanomas (4,10,11), there is still much controversy surrounding the aggressiveness of the array of Spitz lesions in children. Sentinel lymph node biopsy of difficult/indeterminate lesions is one adjunct by which to assess a lesion's aggressive nature (12) and is a standard practice at many institutions. More recently, new molecular studies have revealed that a minority of Spitz tumors have amplifications in chromosome 11p (13) and more commonly have HRAS compared to BRAF or NRAS mutations that are commonly seen in melanoma (4,14). While these may help in guiding diagnostic decision making, they are again only present in a minority of cases.

Given the difficulty in determining the aggressiveness of Spitz lesions/spitzoid melanoma, pediatric patients with positive sentinel node biopsies have been largely managed in the same manner with melanoma of the same stage at the time of this study. The upfront interventions, from surgery/lymph node dissection to interferon therapy, have a range of side effects, some of them long-lasting including mood disturbances and hypothyroidism (15). Interferon alpha therapy has been routinely offered to pediatric patients with stage III/high risk lesions based on data from the adult literature demonstrating a survival advantage in adult melanoma patients receiving interferon (16,17). However, this differs from stage III melanoma therapy in adults where interferon is typically not administered because of the significant side effect profile and limited benefit in that setting. In general, pediatric patients tend to tolerate interferon therapy better when compared to the adult population (9).

With the overall incidence of pediatric melanoma on the rise at about 2% annually (18) and delays in diagnosis potentially leading to disease progression and metastasis requiring aggressive, invasive medical interventions, recognizing these lesions early and accurately is essential. Further, taking steps toward identifying lower risk pediatric patients and minimizing interventions could also lend to decreasing long term morbidity. In this retrospective study, we aimed to determine factors leading to diagnosis delay, side effects and exposures during therapy and overall survival in this patient population. Further, through this analysis we aim to identify points of intervention to be used in future studies to improve the diagnostic process and limit side-effects/exposures in this patient population.

Methods

Study design

The Institutional Review Board (IRB) approved (HUM00050014) University of Michigan Pediatric Oncology "Study of Long Term Outcome of Children and Young Adults with Cancer" database was queried (IRB study approval number HUM00117410) for all cases of pediatric melanoma and high risk atypical melanocytic lesions referred to our clinic for consideration of adjuvant therapy (inclusion criteria included a minimum stage III disease at diagnosis according to the National Comprehensive Cancer Network melanoma guidelines, version 3.2015, or equivalent for spitzoid lesions with positive sentinel lymph node biopsies) over a 13-year time period [2000–2013]. A retrospective chart review of these cases was performed in order to address the specific parameters and outcomes in these patients including presenting features, age, sex, ethnicity, lesion location, time from parental concern noted to presentation to PCP, time from PCP presentation to final diagnosis, histology, genomic data, Clark level, Breslow depth, stage, outside pathological diagnosis, final pathological diagnosis upon expert dermatopathology review at our institution, lymph node status, surgical interventions, presence of lymphedema, presence of scar or keloid, other surgical complications, treatment received, side effects from interferon therapy, use of PJP prophylaxis, other skin lesions biopsied after diagnosis, scans following diagnosis, family history and current patient status. Patient information was de-identified and kept confidential in accordance with the Health Insurance Portability and Accountability Act (HIPAA) standards. Patients referred to our clinic with concerning lesions/lymph node positivity but were found by our multidisciplinary team to have a final diagnosis of pigmented epithelioid melanocytoma (PEM, n=2) were excluded from final survival analyses given the known benign course of these lesions. The PEM patients also did not undergo interferon therapy treatment.

Statistical methods

The Wilcoxon rank-sum test was used to compare time to final diagnosis between two groups (first diagnosed as a wart vs excluding wart primary diagnosis). Overall

Variable	Total number (N) and % total
Total study subjects	N=30, 100%
Sex	
Male	N=14, 47%
Female	N=16, 53%
Ethnicity/race	
Caucasian	N=25, ~83%
African American	N=1, ~3%
Mexican/Hispanic	N=2, ~7%
Other	N=2 (~7%, Native American and no data available)
Age at diagnosis	
Birth to 9 years	N=10, ~33%
10-15 years	N=14, 47%
16 -20 years	N=6, 20%
Pathologic diagnoses	
Melanoma	N=7, ~23%
Nodular melanoma	N=3, 10%
Superficial spreading melanoma	N=2, ~7%
Other	N=1, ~3%
Pigmented epithelioid melanocytoma (PEM)	N=2, ~7%
Aggressive atypical Spitz tumor of uncertain biological potential (S-UBS)	N=15, ~50%
Location of primary lesion	
Head and neck	N=16, ~53%
Extremity	N=10, ~33%
Other	N=4, ~13%

Figure 1 Patient population data from the 30 pediatric patients included in this study from 2000–2013.

patient survival was defined from the date of diagnosis to death of any cause. Data was censored at the last follow-up for patients who were still alive at the time of analysis. Progression-free survival was defined from the date of diagnosis to the earlier date of either disease progression or death. Survival curves were constructed using the Kaplan-Meier method and survival differences were assessed using the log-rank test. Statistical significance was defined as a P<0.05. All analyses were performed using SAS 9.4 software.

Results

The University of Michigan Division of Pediatric Hematology and Oncology saw 30 pediatric patients from 2000 to 2013 with skin lesions that included the following pathologic diagnoses: aggressive atypical Spitz tumor of uncertain biologic potential (~50%), melanoma (~23%), nodular melanoma (10%), superficial spreading melanoma (~7%), PEM (~7%), and other (~3%). A breakdown of the pathologic subtypes and further patient demographic

Table 1 Family history of cancer in the patient population

Documented family history	Total number (N) and % total
No family history of melanoma	N=21, 70%*
Family history of melanoma	N=8, ~27%*
No family history of other cancers	N=9, 30%
Family history of breast cancer	N=7, ~23%
Family history of pancreatic cancer	N=1, ~3%
Family history of mesothelioma	N=1, ~3%
Family history of melanoma and other cancers	N=5, ~17% of total and ~63% of patients with + melanoma family history
Family history of multiple cancers but not melanoma	N=11, ~37%

*, one patient was adopted and the family history for that one patient is unknown.

information is detailed (*Figure 1*).

Briefly, there was a near-even distribution of males versus females (1 to 1.14), which is consistent with the SEER (Surveillance, Epidemiology, and End Results) data for pediatric melanomas (18). The majority (approximately 83%) of the patients were Caucasian and the approximate mean age at the time of diagnosis was 11 years. The head and neck (~53%) and extremity (~33%) were the most common location of primary lesions. As about 10% of melanomas are thought to be hereditary (19) and there are reported familial cancer syndromes including melanoma, we also analyzed documented family histories for relevant associations such as other family members with melanoma, pancreatic cancer [given links with CDKN2 mutations (20)], breast cancer and mesothelioma (21,22) (*Table 1*). Most patients in this study had no significant family history suggestive of a familial cancer syndrome, but one familial syndrome was discovered out of the 30 patients reviewed. This family was referred to genetics for further risk assessment and long-term management. There were no obvious links with the obtained family histories and patient outcomes in this study. Family history data for 29 of 30 pediatric patients included in this study, as the remaining patient was adopted and therefore no family history was available.

Upon analyzing the initial presenting skin lesion features, we noted that lesion growth, bleeding, and itching were the most common reasons why children were taken
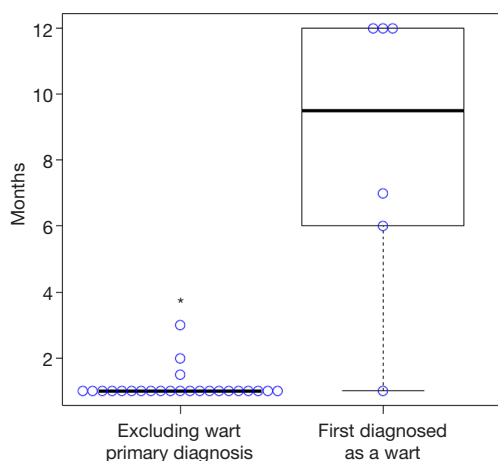
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Figure 2 Box plot of time to final diagnosis (in months) when comparing lesions lacking dark pigment and initially diagnosed as a wart versus not. *, P=0.00011.
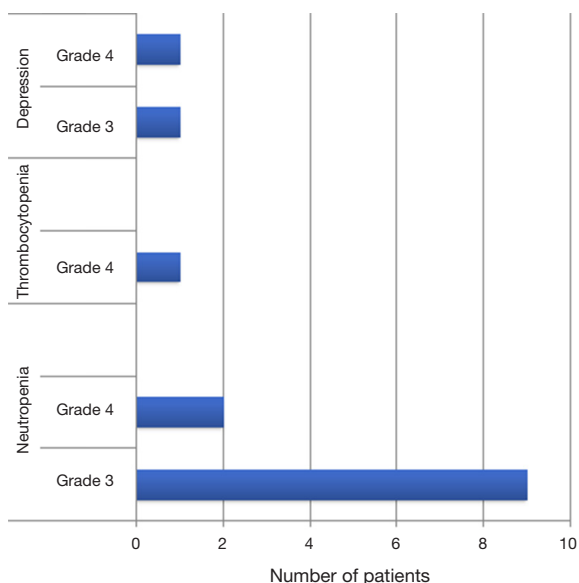

Figure 3 Number of patients experiencing Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and 4 toxicities while receiving interferon therapy.

to their primary pediatricians for evaluation. In contrast to the "classic" darkly pigmented lesions, melanomas can also present with amelanotic or flesh-colored lesions in both pediatric and adult populations. Six of our thirty patients had such lesions lacking pigment and these six lesions were all initially misdiagnosed as warts. The patients with amelanotic lesions were treated with multiple rounds of wart

therapies such as liquid nitrogen prior to a biopsy being performed. In our patient population, initial misdiagnosis led to significant delays in the diagnosis of melanoma or atypical melanotic lesions compared to lesions not labeled as a wart in the primary care setting (P=0.00011, *Figure 2*). The median time of diagnosis delay in the amelanotic group was greater than 9 months. Of the patients initially clinically diagnosed with warts, four had a pathological diagnosis of a S-UBS and two were diagnosed with melanoma. We next analyzed the pathologic data to look for changes in diagnosis upon expert pathology review. In this series of thirty patients, two (6–7%) had changes in diagnosis. Six other patients were noted to be very challenging cases from a pathology perspective and requested second opinions prior to establishing a final diagnosis.

All patients were considered for interferon alpha therapy, a common practice in pediatric oncology during this study period based on adult literature demonstrating a survival advantage (16). Twenty-six patients received interferon alpha therapy. The four patients that did not receive interferon included patients with the final diagnosis of PEM [reported to be a very benign behaving lesion with excellent clinical outcomes despite frequent lymph node involvement (23,24)], a patient that was non-compliant with follow-up and one patient with rapid disease progression. Those patients receiving interferon alpha therapy were planned to received 4 weeks of high dose IV interferon (20 million units/m^2, 5 days weekly) followed by 48 weeks of low dose subcutaneous interferon (10 million units/m^2, 3 days weekly). Noted side effects documented from interferon therapy included but were not limited to fevers, chills, myalgias, headache, nausea, fatigue, weight loss, transaminitis, hair loss, mood disturbances, Bell's Palsy and pain. Interferon dose adjustments or discontinuation in our patient population were implemented for side effects including neutropenia, thrombocytopenia, and depression/anxiety (mood disturbances). The number of patients experiencing and grades of severity (based on Common Terminology Criteria for Adverse Events, CTCAE) of these side effects are in *Figure 3*. The majority of dose reductions occurred during high dose interferon therapy (the first four weeks). Five patients experienced abnormal thyroid studies but none required dose modifications. As noted in *Figure 4A*, 7 of 13 patients with the diagnosis of melanoma and 14 of 15 patients with S-UBS completed 52 weeks of interferon therapy without dose reduction or drug discontinuation.

We then examined both the side effect burden (taking into consideration all aspects of therapy including surgical

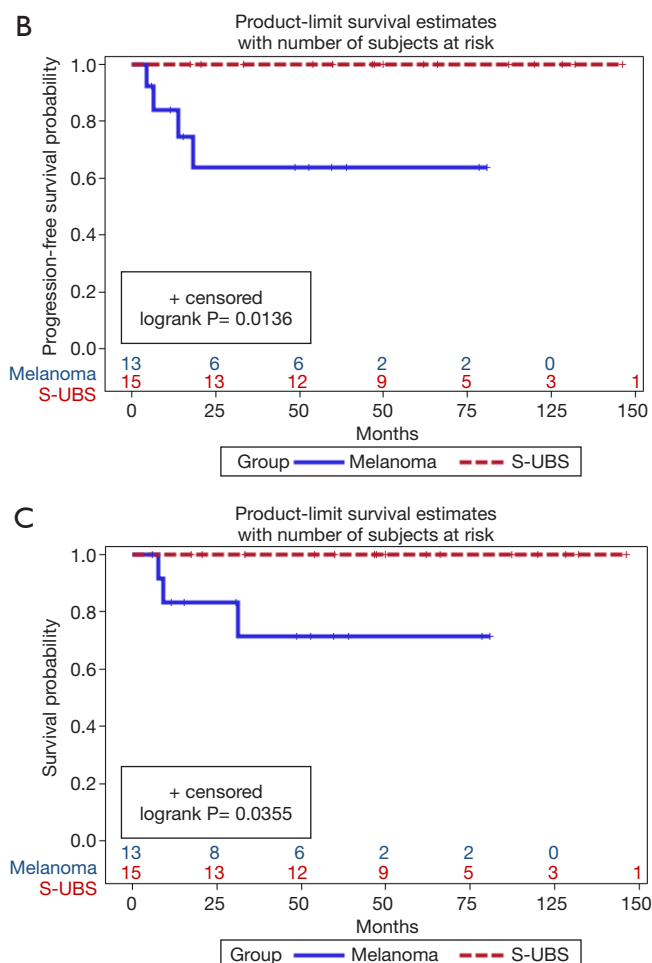| A	Melanoma (total cases, n=13)	S-UBS (total cases, n=15)
Patient Sex		
Male	6	6
Female	7	9
Lesion Characteristic		
without pigment/'colorless'	3	3
bleeding	5	6
itching	6	1
enlarging in size	7	11
Surgical Management		
wide local excision	12	15
sentinel node biopsy	11	14
regional lymph node dissection	11	14
Post-Surgical Complications		
scar (requiring intervention)	4	5
lymphedema (requiring intervention)	3	4
pain (persistent)	4	2
Other skin lesions biopsied		
average number of other lesions biopsied	2	1.53
biopsies positive for melanoma	0	0
Interferon Therapy		
patients receiving full 52 weeks of interferon therapy	7	14
experienced side effect requiring interferon dose reduction or discontinuation	5	3
Other complications around treatment		
hospitalization for infection	0	2
Scans Obtained Post-Diagnosis (average)		
PET	1.15 (range 0-4)	0.5 (range 0-3)
CT	1.38 (range 0-3)	1.3 (range 0-10)
CXR	0.46 (range 0-1)	1.2 (range 0-4)
Outcomes		
recurrence	4	0
death	3	0

Figure 4 Variable comparison between patients with a confirmed diagnosis of melanoma versus atypical Spitz tumor of uncertain biological potential (A). Plot of progression-free (B, P=0.0136) and overall survival (C, P=0.0355) for the melanoma and aggressive Spitz tumors of undetermined biological significance (S-UBS) patients in this study.

management (25,26), surgical complications, interferon therapy, radiation exposure due to scans, etc.) and the overall survival of patients with S-UBS versus melanoma patients in our population. Patients with PEM were excluded from the analyses, given the benign nature of these lesions and the fact that these patients did not receive interferon therapy (as discussed previously). *Figure 4A* compares the melanoma versus S-UBS groups for differences in variables including patient sex, lesion characteristics, surgical management, post-surgical complications, other skin lesions biopsied, interferon therapy, other treatment complications, surveillance scans, and outcomes. There was an even distribution of male and female cases in each group. Regarding lesion characteristics, itching was reported more commonly in patients diagnosed

with melanoma versus S-UBS (6 *vs.* 1 patient, respectively). Surgical complications including lymphedema, scar formation and pain were comparable between the two groups. Both groups had similar numbers of subsequent lesions biopsied, none revealing melanoma. Seven of 13 patients (~54%) of melanoma patients and 14 of 15 (~93%) of S-UBS completed 52 weeks of interferon therapy without interruption (dose reduction or drug discontinuation). Two S-UBS patients were hospitalized for infections while PICC lines were in place (around the time of high dose interferon therapy). Disease monitoring with scans revealed great variability both in the number and type of scans ordered. This appeared to be due to individual physician preference. On scans performed at the end of interferon therapy, one melanoma patient was noted to have new lung lesions, later

confirmed to be new metastatic disease. None of the scans obtained in the S-UBS patients were positive for disease/new lesions.

Lastly, we examined progression free and overall survival based on diagnosis. A significant difference in progression-free (*Figure 4B*) and overall survival (*Figure 4C*) was noted, with the S-UBS group having no patients demonstrating progression (P=0.0136) or death (P=0.0355), while the melanoma group had four patients progress, with three of these eventually passing away from disease. None of the patients with delayed diagnoses due to a "wart-like" appearance of their lesions progressed or passed away (again, this group included both melanoma and S-UBS patients). One of the patients whose pathological diagnosis was notably challenging upfront (and required expert pathology review to establish a final diagnosis) was one of the three that passed away.

Discussion

Pediatric patients with aggressive S-UBS and melanoma continue to be a rare and very challenging patient population. Given the possibility of familial cancer syndromes in such patients (one identified in this study), a detailed cancer history should be obtained. With the presence of clear side effects from both the medical and surgical interventions surrounding the diagnosis and treatment of pediatric melanomas and S-UBS, it is of critical importance to prevent diagnosis delays as much as possible in order to minimize the amount of interventions required and to accurately triage these patients upfront. This study revealed that in our pediatric patient population, lesions being incorrectly labeled and treated as warts lead to a significant delay in diagnosis. While this is a difficult visual diagnosis, typically warts have thrombosed capillaries and interrupt skin lines while more concerning lesions often have "red flag" features such as itching. This "wart-like" appearance does not discriminate between melanomas and S-UBS. While none of these patients misdiagnosed as warts died, it is possible that if diagnosed earlier, the disease may have not been staged as high and these patients could have been spared some interventions (further lymph node dissection, interferon treatment, or exposure to radiation for scans for disease detection or monitoring). We feel that continued education of primary care providers about such lesions could be a key intervention to prevent delays. As warts are far more common than melanoma in

pediatrics, we propose that if warts have corresponding lack of response to therapy, lesion growth, bleeding, or itching, that these patients be promptly biopsied prior to continuing wart therapy.

A second issue noted was the initial pathological misdiagnosis or diagnostic uncertainty surrounding these cases. Eight of the thirty cases (~27%) were documented to be challenging pathology cases and did result in some changes in diagnosis. This fact highlights the point that it is essential upfront for expert case review to be sought out in these pediatric cases.

A patient management point that was discovered during our analysis is the high variability in the types and frequency of scans for monitoring this cohort of patients. While some patients only received scans upfront, half-way and the end of therapy, other patients had scans at more frequent intervals. Patients were monitored with chest X-rays, CT scans, PET scans or some combination of these. Only one patient with a diagnosis of melanoma had asymptomatic new metastatic lesions that were noted on end of therapy scan only. There is a lack of consensus in the pediatric literature pertaining to the type and frequency of scans in these patients. Given that in general, limiting radiation exposure in children is a priority and the fact that S-UBS patients do well and likely would not need scans for monitoring at any point, forming consensus recommendations for imaging in this patient population will be a future priority.

With the controversy surrounding the aggressiveness of spitzoid lesions, the survival data obtained from our single center study suggests that even patients with histologically aggressive/lymph node positive S-UBS have very favorable outcomes and the role of adjuvant therapy as well as imaging for surveillance in these patients needs to be examined in the future in a prospective multi-institutional study. On the other hand, true pediatric melanomas showed aggressive clinical behavior and mortality similar to their adult counterparts despite interferon therapy (27). New investigational approaches are desperately needed and agents recently approved for adult melanoma, including B-RAF inhibitors, MEK inhibitors, CTLA-4 inhibitors and PD-1 inhibitors (28-30) need to be tested either as a single agent or as combination therapy.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The Institutional Review Board (IRB) approved (HUM00050014) University of Michigan Pediatric Oncology "Study of Long Term Outcome of Children and Young Adults with Cancer" database was queried (IRB study approval number HUM00117410) for all cases of pediatric melanoma and high risk atypical melanocytic lesions referred to our clinic for consideration of adjuvant therapy (inclusion criteria included a minimum stage III disease at diagnosis according to the National Comprehensive Cancer Network melanoma guidelines, version 3.2015, or equivalent for spitzoid lesions with positive sentinel lymph node biopsies) over a 13-year time period [2000–2013].

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