A retrospective multicenter study of fatal pediatric melanoma

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Background: Pediatric melanoma is rare and diagnostically challenging.

Objective: To characterize clinical and histopathologic features of fatal pediatric melanomas.

Methods: Multicenter retrospective study of fatal melanoma cases in patients younger than 20 years diagnosed between 1994 and 2017.

Results: Of 38 cases of fatal pediatric melanoma identified, 57% presented in white patients and 19% in Hispanic patients. The average age at diagnosis was 12.7 years (range, 0.0-19.9 y), and the average age at death was 15.6 years (range, 1.2-26.2 y). Among cases with known identifiable subtypes, 50% were nodular (8/16), 31% were superficial spreading (5/16), and 19% were spitzoid melanoma (3/16). One fourth (10/38) of melanomas arose in association with congenital melanocytic nevi.

Limitations: Retrospective nature, cohort size, and potential referral bias.

Conclusions: Pediatric melanoma can be fatal in diverse clinical presentations, including a striking prevalence of Hispanic patients compared to adult disease, and with a range of clinical subtypes, although no fatal cases of spitzoid melanoma were diagnosed during childhood. (J Am Acad Dermatol 2020;83:1274-81.)

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CAPSULE SUMMARY

- This study characterizes clinical and histopathologic features of fatal pediatric melanomas.
- Pediatric melanoma can be fatal in diverse clinical presentations, including a striking prevalence of Hispanic patients, and across clinical subtypes, although no fatal cases of spitzoid melanoma were diagnosed during childhood.

Melanoma in the pediatric population is far rarer than in adults.[1-3] Adolescent disease has an annual incidence of 18 cases per 1 million individuals aged 15-18 years, whereas prepubertal disease is even more rare, with an incidence rate of approximately 1 case per 1 million children younger than 10 years.[3] Melanoma in children and adolescents often has distinct clinical presentations, such as association with a congenital melanocytic nevus (CMN), spitzoid melanoma, or amelanotic melanoma, which are more rarely observed in adult patients with melanoma.[4-6] Unique pediatric-specific clinical detection criteria have been proposed to highlight these differences, such as a tendency to present amelanotically.[5,6] The Breslow thickness and mitotic index upon diagnosis of pediatric melanoma are often higher than in adult melanoma, particularly for childhood melanoma (diagnosed at age <11 y) as compared to adolescent disease.[7,8] It is unclear if this difference is secondary to diagnostic delays due to low clinical suspicion, atypical clinical presentations, or more rapid tumor growth rate, because many childhood melanomas are of nodular or spitzoid subtypes.[9] Diagnosis is based on histopathologic features and can be challenging, often defying consensus among expert dermatopathologists.[10]

Given the rarity of pediatric melanoma, it is important to evaluate fatal cases to identify clinical and histopathologic features that characterize the most aggressive subsets. Furthermore, given the difficulties in reaching diagnostic consensus in cases of pediatric melanoma, a description of fatal cases may facilitate characterization of pediatric melanoma in the least ambiguous cases and avoid the limitations of diagnostic uncertainty that are often raised in reports of patients with pediatric melanoma. It is vital to classify pediatric melanoma to distinguish spitzoid, conventional (or adult-type), and CMN-associated melanomas because of their distinct presentations, genetics, and clinical courses. An improved understanding of the clinical and histopathologic features associated with fatal disease can help inform prognosis and management of pediatric patients with melanoma. This study retrospectively analyzed cases of fatal pediatric melanoma from academic centers internationally to characterize the most aggressive clinical presentations.

METHODS

This was a multicenter, retrospective study of pediatric patients with melanoma diagnoses with fatal outcomes and was approved by the Dana-Farber Cancer Institute institutional review board (15-156). Inclusion criteria included melanoma diagnosed at 20 years of age or younger, melanoma diagnosed between September 1, 1994, and January 1, 2017, and confirmed death. Patients without relevant medical records were excluded. This patient cohort was established through recruitment of dermatologists affiliated with the Pediatric Dermatology Research Alliance and collaborators.

Seven of 11 centers in the Pediatric Dermatology Research Alliance Pediatric Melanoma Study Consortium had at least 1 case that met diagnostic criteria; analysis of nonfatal cases and risk factors is undertaken separately. This cohort was expanded to include an additional 18 patients from 5 other academic centers, totaling 38 cases from 12 academic centers. Four of the cases reported were described in other publications on this topic.[11,12]

Descriptive analyses were performed to summarize the number and proportion of patients by demographics, tumor characteristics, and clinical management. No inferential testing was performed. Analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Demographics

Thirty-eight cases of fatal pediatric melanoma were identified from 12 academic centers; 4 other academic centers queried had no cases of fatality. Of the 38 cases, 42% were male and 58% female patients; 57% of patients were white, and 19% were Hispanic (Table I). Of the cases with reported skin phototypes, two thirds (8 of 12) of patients had Fitzpatrick skin type I or II.

There was history of blistering sunburns in 15% (2/13) of patients with available data. A history of tanning bed use was present in 6% (1/17) of patients with available data. A positive family history of

Abbreviations used:

CMN: congenital melanocytic nevus
FISH: fluorescent in situ hybridization
LVI: lymphovascular invasion
SD: standard deviation
SLNB: sentinel lymph node biopsy

melanoma in a first-degree or distant relative was reported in 10% (3/30) and 12% (3/25) of patients, respectively (Table II).

Age and CMN association

The average age at diagnosis was 12.7 years (standard deviation [SD], 6.3), with a median age of 15.2 years and a range of 0 to 19.9 years. Of the 38 cases, 24% were diagnosed during childhood (age <11 y) and 76% during adolescence (age 11-20 y). The average age at death was 15.6 years (SD, 7.1), with a median of 17.7 years and range of 1.1 to 26.2 years. Patients survived an average of 35 months (SD, 29.7) from the time of diagnosis (Table I). Average survival time for the patients with spitzoid melanoma was 23.0 months after diagnosis.

About one fourth (10/38) of melanomas arose from a CMN (Table III), most of which (5/6 with known size) were clinically identified as large (≥20 cm projected adult size) or giant (≥40 cm projected adult size) CMNs. Among the 10 CMN-associated melanoma cases, half were diagnosed in adolescence (age range, 13-19 y) and half in childhood (age range, 0-6 y). Four of 5 childhood CMN-associated cases were diagnosed in the first 2 years of life (Fig 1). In all 5 cases of CMN-associated melanoma that reported associated smaller accompanying CMNs (previously termed *satellites*"),[13] melanoma developed within the largest CMN. Two CMN-associated cases developed in patients with neurocutaneous melanocytosis, hydrocephalus, and ventriculoperitoneal shunt; of these, 1 case of melanoma occurred within the central nervous system and the other within the CMN (patients 5 and 9, respectively) (Table II).

Prior medical history

Only 1 patient in the cohort had a predisposing genetic condition noted in the medical record, xeroderma pigmentosum. Of 37 patients with available medical history data, none had prolonged immunosuppression (>6 months), and 3 of 34 had a known prior malignancy. One patient had a giant CMN and rhabdomyosarcoma before the development of melanoma; the rhabdomyosarcoma was treated with localized radiation therapy and 11 months of chemotherapy, and the subsequent melanoma developed outside the site of previous radiation therapy.

Table I. Demographics of patients with fatal pediatric melanoma (N = 38)

Characteristics	Values
Age at diagnosis, y, mean (SD); median (range)	12.7 (6.3); 15.2 (0-19.9)
Age at death, y, mean (SD); median (range)	15.6 (7.1); 17.7 (1.2-26.2)
Survival time after diagnosis, mo, mean (SD)	35.0 (29.7)
Age at diagnosis, n (%)	
Childhood (<11 y old)	9 (24)
Adolescence (≥11 y old)	11 (76)
Sex, n (%)	
Male	16 (42)
Female	22 (58)
Race, n (%)	
White	21 (57)
Hispanic/Latino	7 (19)
Asian	1 (3)
Black or African American	1 (3)
Black or African American and Hispanic/Latino	1 (3)
Other	6 (16)
Not recorded	1
Fitzpatrick skin type, n (%)	
I-II	8 (67)
III-IV	3 (25)
V-VI	1 (8)
Not recorded	26

SD, Standard deviation.

Clinical characteristics

Clinical lesional evolution was documented in all 19 cases reporting on this parameter. Asymmetry was observed in 17% of documented cases (1/6), border irregularity in 14% (1/7), color variegation in 70% (7/10), and diameter of 6 mm or greater in 100% (6/6). One of 12 cases (8%) was reported as amelanotic (8%), 88% (14/16) were raised, and 55% (6/11) exhibited bleeding (Table III).

The most common locations among the 30 melanoma cases with available data included the back (n = 8), scalp (n = 6), face (n = 4), and arm (n = 3) (Table II). Among the 37 patients with available data, 10 (27%) had a general history of atypical nevi, 2 (5%) had a history of lentigos, and 26 (70%) reported no prior skin diseases (Table III).

Histopathologic features and management

Of 16 patients with reported histopathologic subtypes, 50% were nodular (n = 8), 31% were

Table II. Cohort characteristics

Patient	Age at diagnosis, y	Age at death, y	Sex	Race	Associated medical conditions	Family history*	Year of diagnosis	Location	Melanoma subtype	Breslow thickness, mm	Ulceration	Mitotic index per mm^2	Tumor genetic testing	SLNB	Metastases	Treatment other than excision
CMN associated																
1	0.0	1.2	M	White	CMN	NR	2014	Back	Unclassified	8	Yes	NR	Not done	+	Distant	NR
2	1.0	4.9	F	NR	CMN	-	1998	Scalp	Unclassified	8	No	18	Not done	+	Distant	IFN Vaccine therapy
3	1.7	2.5	F	Hispanic/ Latino	CMN	-	2008	Back	Nodular	5	No	7	G-banding performed	+	Distant	IFN IL-2 Checkpoint inhibitor
4	1.8	1.9	M	African American	CMN	NR	2015	Face	Unclassified	NR	NR	NR	*BRAF* negative	NR	NR	Chemotherapy
5	6.1	6.4	F	White	CMN, NCM, hydrocephalus + shunt	NR	2009	NR	Indeterminate	NR	NR	NR	Not done	None	Distant	Radiation
6	13.1	14.4	F	White	CMN, type I diabetes	-	2002	Back	Spitzoid	1.67	No	3	Not done	+	Distant	Radiation Chemotherapy IFN
7	14.9	15.6	M	Asian	CMN, rhabdomyosarcoma, chemo/rad	-	2008	Anogenital region	Unclassified	NR	NR	NR	CGH performed†	-	Distant	NR
8	16.5	19.2	F	African American, Hispanic/ Latino	CMN	-	2011	Anogenital region	Unclassified	12	Yes	12	*BRAF* positive	+	Distant	IFN BRAF inhibitor Checkpoint inhibitor
9	18.9	19.4	M	Hispanic/ Latino	CMN, NCM, hydrocephalus + shunt	-	2007	Back	Nodular	10	Yes	"High"	Not done	None	Distant	Radiation Chemotherapy
10	19.9	22.5	F	White	CMN, chronic abdominal pain	-	2012	Back	Unclassified	7	Yes	30	*BRAF* positive	+	Distant	Radiation BRAF inhibitor Checkpoint inhibitor
No CMN association																
11	0.3	2.3	F	White	None	+	2011	Abdomen	Unclassified	NR	Yes	Numerous	*BRAF* positive	None	Distant	Radiation BRAF inhibitor
12	1.4	1.6	F	Hispanic/ Latino	None	NR	2008	NR	Unclassified	NR	NR	NR	NR	NR	Distant	NR
13	3.2	5.3	F	NR	NR	NR	2001	NR	Unclassified	NR	NR	NR	NR	NR	Distant	Radiation Chemotherapy Alteplase clinical trial
14	6.0	13.3	M	Hispanic/ Latino	Roberts syndrome	-	2010	Face	Unclassified	NR	NR	NR	Not done	NR	None	NR
15	11.5	16.0	F	White	None	NR	2000	Arm	Unclassified	36	No	10	NR	+	Distant	Chemotherapy IFN IL-2 Checkpoint inhibitor Vaccine therapy GM-CSF‡
16	11.5	19.8	F	NR	None	-	2003	Arm	Unclassified	0.9	No	NR	*BRAF* negative	-	Distant	Chemotherapy Checkpoint inhibitor IL-2 Tumor-infiltrating lymphocyte harvesting and fusion
17	11.8	12.5	F	Hispanic/ Latino	None	-	2008	NR	Unclassified	NR	NR	NR	G-banding performed	None	NR	Radiation Chemotherapy
18	13.8	19.9	F	Race not recorded, SPT I-II	Xeroderma pigmentosa	-	2006	Face	Superficial spreading	0.9	No	20-40	*XPA* mutation of unknown significance	+	Distant	Radiation IFN

Continued

Table II. Cont'd

Patient	Age at diagnosis, y	Age at death, y	Sex	Race	Associated medical conditions	Family history*	Year of diagnosis	Location	Melanoma subtype	Breslow thickness, mm	Ulceration	Mitotic index per mm^2	Tumor genetic testing	SLNB	Metastases	Treatment other than excision
19	13.9	17.1	M	White	None	-	2002	Neck	Superficial spreading	1.9	No	NR	Not done	-	Distant	Radiation Chemotherapy IFN IL-2
20	14.8	24.3	M	White	NR	NR	1994	Scalp	Nodular	2.2	NR	NR	NR	NR	Distant	IFN
21	15.0	17.8	F	White	NR	-	2011	Face	Unclassified	NR	NR	NR	Not done	None	Distant	NR
22	15.0	18.0	F	Race not recorded, SPT I-II	None	-	2000	Abdomen	Superficial spreading	1.2	Yes	3	NR	-	Distant	Craniotomy for brain metastases
23	15.4	17.6	M	Hispanic/ Latino	None	-	2009	Scalp	Superficial spreading	1	NR	2	*BRAF* positive	+	Distant	Radiation Chemotherapy IFN Checkpoint inhibitor
24	15.6	19.3	M	White	None	-	2000	Arm	Nodular	17.2	No	5	NR	-	Distant	Radiation IFN
25	15.6	19.3	F	NR	None	NR	2006	Back	Spitzoid	1.48	NR	NR	CGH performed§	+	Distant	Radiation IFN IL-2
26	15.7	16.8	F	White	None	+	2005	NR	Unclassified	NR	NR	NR	FISH and CGH with multiple losses/gains‖	NR	Distant	Radiation Chemotherapy IFN IL-2
27	15.7	17.5	F	White	None	-	2007	Scalp	Indeterminate	NR	Yes	NR	Not done	-	Distant	IL-2
28	15.8	16.7	F	Hispanic/ Latino	None	-	2017	NR	Unclassified	NR	NR	NR	Not done	None	Regional	Radiation Chemotherapy Checkpoint inhibitor
29	16.1	20.0	F	White	None	-	2000	Chest	Unclassified	1.5	No	1	NR	+	Distant	IFN
30	16.3	16.9	M	White	None	NR	2010	NR	Indeterminate	NR	No	NR	NR	None	Distant	Chemotherapy
31	17.3	20.0	M	White	None	-	2004	Back	Nodular	3.75	No	4	Not done	+	Distant	Radiation IFN
32	17.3	24.0	M	White	None	-	2009	NR	Nodular	4.3	No	2	*BRAF* positive	+	Distant	Radiation IFN BRAF inhibitor
33	17.5	23.3	M	White	None	-	2004	Scalp	Nodular	3.5	No	10	*BRAF* positive	+	Distant	Radiation Chemotherapy IFN IL-2 BRAF inhibitor
34	17.8	19.9	M	NR	None	-	2012	Back	Unclassified	2.2	Yes	30	*BRAF* positive, *NRAS* negative	-	Distant	Radiation BRAF inhibitor Checkpoint inhibitor
35	18.1	20.4	M	White	None	-	1999	Scalp	Unclassified	2.1	No	1	Not done	+	Local	IFN
36	18.5	26.2	F	White	None	-	2008	Chest	Superficial spreading	1.7	No	2	FISH and MSK profile performed¶	-	Distant	BRAF inhibitor Checkpoint inhibitor
37	19.3	20.2	M	White	None	-	2009	Ear	Nodular	6	Yes	3	Not done	+	Distant	Radiation Chemotherapy
38	19.8	20.4	F	White	None	+	2005	Leg	Spitzoid	1.1	No	3	Not done	None	Distant	Chemotherapy

CGH, Comparative genomic hybridization; *chemo/rad*, chemotherapy and radiation; *CMN*, congenital melanocytic nevus; *F*, female; *FISH*, fluorescent in situ hybridization; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *IFN*, interferon; *IL*, interleukin; *M*, male; *MSK*, Memorial Sloan Kettering; *NCM*, neurocutaneous melanocytosis; *NR*, information not recorded in the medical record; *SLNB*, sentinel lymph node biopsy; *SPT*, skin phototype.

*Family history denotes first-degree family.

†CGH showed loss of short arm 1, loss of long arm 6, and gain of short arm 6.

‡Autologous GM-CSF–secreting cell therapy.

§CGH showed loss of chromosome 9 and chromosome 10, and gain in chromosome 7.

‖FISH: pseudohyperduploidy chromosome 52; CGH: loss of chromosome X; chromosome 1 tetrasomy; trisomies 3, 6, 8, 13, 16, and 22; tetrasomy chromosome 20; nullisomy chromosome 10; and 2 abnormal chromosome 15s.

¶FISH with 3 copies of *EWSR1*; MSK profile: *BRAFV600E, PIK3CA, PTEN, CDKN2B, CDKN2Ap16INK4A, CDKN2A p14ARF, PRDM1, FYN, ROS1, CRLF2, ANKRD11, HLA-A, TERT.*

Table III. Tumor characteristics in cases of fatal pediatric melanoma (N = 38)

Tumor characteristics	Values
Subtype, n (%)	
Nodular	8 (50)
Superficial spreading	5 (31)
Spitzoid	3 (19)
Not identified or reported	22
Patient with CMN, n/total (%)	10/38 (26)
CMN of origin, large/giant	5/6 (83)
Arose from satellites	0/5 (0)
Metastasis, n (%)	
Distant metastasis	33 (92)
Local/regional metastasis	2 (6)
None	1 (3)
Not recorded	2
Clinical features, n/total (%)*	
Asymmetry	1/6 (17)
Border irregularity	1/7 (14)
Color variegation	7/10 (70)
Color homogeneity	0/9 (0)
Diameter of ≥6 mm	6/6 (100)
Evolution	19/19 (100)
Amelanotic	1/12 (8)
Raised	14/16 (88)
Bleeding	6/11 (55)
Arising de novo	4/12 (33)
Arising from a nevus	13/18 (72)
Presence of prior skin disease, n (%)	
Atypical nevi	10 (27)
Lentigos	2 (5)
None	26 (70)
Not recorded	1
Breslow thickness, mm, median (range)	2.2 (0.9-36.0)
Mitotic rate per mm^2, median (range)	3.5 (1.0-30.0)

CMN, Congenital melanocytic nevus.
*The denominator used is the number of patients in whom a particular clinical feature was assessed.

superficial spreading (n = 5), and 19% were spitzoid (n = 3). In 22 cases, a conventional histopathologic subtype could not be identified (n = 14) or was not reported (n = 8) (Table III). The 3 identified spitzoid melanoma cases were diagnosed at ages 13, 15, and 19 years, the youngest of which was associated with a CMN.

Among 25 cases with reported tumor depths, the median Breslow thickness was 2.2 mm, with a range of 0.9 to 36 mm. Of the 18 cases reporting on mitotic rates, the median mitotic rate was 3.5 per mm^2, with a range of 1 to 30 per mm^2. Ulceration was present in 36% of cases (9/25) and lymphovascular invasion (LVI) in 28% (5/18).

Metastases were observed in 97% of cases: distant metastasis was observed in 92% (33/36) of cases with known data and locoregional metastasis in 6% (2/36). Sentinel lymph node biopsy (SLNB) was performed in 72% (23/32) of cases and was positive in 70% (16/23). A completion lymphadenectomy was performed in 64% of 33 cases with available data. Of the 3 spitzoid melanoma cases (all adolescents), SLNB was performed in 2 and results were positive in both cases, with subsequent completion lymphadenectomies.

Tumor genetic testing was performed in 53% of cases (16/30) that reported on testing. *BRAF* testing was most common and results were found to be positive in 7 of 9 cases (78%): 2 of 3 CMN-associated cases and 5 of 6 cases not associated with CMN. Comparative genomic hybridization showed chromosomal aberrations in all 3 tumors tested, 1 of which was a spitzoid melanoma. Another patient in whom comparative genomic hybridization was performed also underwent fluorescent in situ hybridization (FISH), which showed pseudohyperdiploidy. FISH was also performed in a second patient who also underwent mutation profiling, revealing 3 copies of *EWSR1*. G-banding was performed in 2 patients (Table II). Treatments included surgical management, interferon, chemotherapy, radiation, checkpoint inhibitors, targeted therapies, and clinical trials (Table II and Table IV).

DISCUSSION

Pediatric melanoma has diverse clinical presentations, a variety of which can be aggressive and ultimately result in death.

The demographic composition of this cohort represents notable differences compared to that seen in adult melanoma. Unlike adult disease,[14,15] only about one half of the patients in this cohort were white, and about one third had skin phototype III or greater. Our cohort, although small in size, shows that fatal pediatric melanoma may occur in a diverse presentation of race and skin type. This is notably different than the demographic data reported in adults and is consistent with Surveillance, Epidemiology, and End Results–based reports showing the growing representation of Hispanic patients with pediatric melanoma.[16]

Three quarters of the patients in this cohort were diagnosed with melanoma in adolescence. Adolescent melanoma in general has been shown to have a more aggressive disease course compared to childhood-onset disease.[11] Of the 9 childhood melanomas in this cohort, 5 were associated with CMN. Four of the 5 childhood cases were associated with large or giant CMN (≥20 cm); the fifth was associated with a medium-sized CMN (1.5-20 cm).

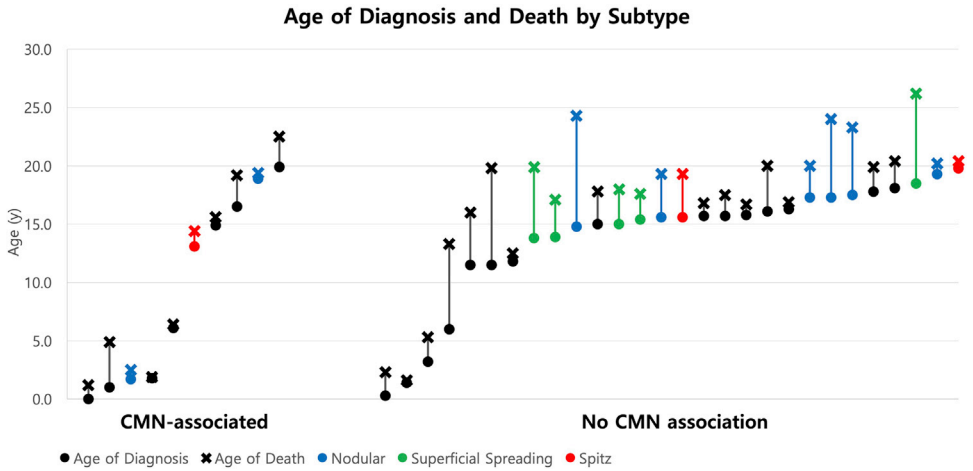

Fig 1. Age at diagnosis and death based on CMN association. Cases are grouped based on CMN association and displayed in increasing order of age at diagnosis. Subtypes are indicated by color, with black denoting an indeterminate subtype. *CMN*, Congenital spitzoid melanoma.

Table IV. Clinical management of cases of fatal pediatric melanoma (N = 38)

Case characteristics	n or n/total* (%)
Tumor genetic testing performed†	16/30 (53)
BRAF	9 (56)
FISH	2 (13)
CGH	3 (19)
Other (mutation analysis)	5 (31)
Lymph node status	
SLNB performed	23/32 (72)
SLNB positive result	16/23 (70)
Lymphadenectomy	21/33 (64)
Adjuvant treatment	
Chemotherapy	15/37 (41)
Radiation	19/37 (51)
Interferon	17/37 (46)
Other immunotherapy (checkpoint inhibitor, IL-2)	14/37 (38)

CGH, Comparative genomic hybridization; *FISH*, fluorescent in situ hybridization; *IL-2*, interleukin 2; *SLNB*, sentinel lymph node biopsy.

*The denominator used is the number of patients in whom a particular clinical feature was assessed.

†Individual genetic testing and results are provided in Table II.

All but 1 of the 5 CMN-associated childhood melanomas were diagnosed in the first 2 years of life. This suggests that early melanomas in at-risk patients have an aggressive course.[17]

Histopathologic review showed that 28% of cases with available data had LVI. LVI in our cohort was observed at a much higher rate than that seen in adult disease, where LVI has been more highly associated with thick tumors.[18,19] These findings suggest that LVI should be carefully evaluated in pediatric melanoma, perhaps with the use of dual staining, given the prevalence of LVI in our cohort.

Only 3 of 38 fatal melanomas were diagnosed as spitzoid melanoma type, and the general term *spitzoid melanoma* is used based on the 2018 World Health Organization classification, in which a subset of spitzoid melanomas with characteristic *HRAS* mutation or kinase fusions is termed *Spitz melanoma*.[4,20,21] It is important to note that none of the spitzoid melanoma cases were diagnosed in childhood; the youngest case was diagnosed at age 13 years and was associated with a CMN. Differentiation between spitzoid melanoma and atypical Spitz tumors is challenging and often debated. Differentiation between the 2 is often determined by the extent and number of atypical features present, but truly unambiguous distinction of these entities is impossible without clinical evidence of metastasis or death.[4,22-24] The older age at onset of the 3 patients with fatal spitzoid melanoma in this cohort, which spanned decades across many large institutions, may be reassuring to prepubertal patients who are diagnosed with Spitz tumors of uncertain malignant potentials. These data beg consideration when weighing the utility of SLNB or completion lymphadenectomy in prepubertal patients with indeterminate Spitz tumors.

The role of SLNB and completion lymphadenectomy in pediatric melanoma in general has been controversial. In our study, 72% of patients had an SLNB, which was positive in 70%, and completion lymphadenectomy was performed in 64% of cases. We expect that these morbid procedures are not necessarily pursued in pediatric patients, particularly

in cases where distant metastases were already identified, as was seen in 92% of this cohort.

Although the majority of patients in the cohort underwent some type of adjuvant treatment in addition to excision, treatments varied greatly; this heterogeneity in management is in part due to the evolution of therapeutic options available during the course of the 2 decades of focus of this study.

These data are affected by a referral bias, because they include cases sent to major academic centers and institutions with specialty clinics. This study is also limited by the cohort size and lack of reporting for some clinicopathologic variables. It is important to recognize that large or prospective studies in pediatric melanoma and, in particular, in the most aggressive subsets presented here are not feasible given the rarity of the disease. Nonetheless, description of these rare cases is vital to allow for better characterization of fatal pediatric melanoma and to improve risk stratification of melanoma in children and adolescents.

Here, we present the largest reported data set, to our knowledge, of fatal pediatric melanoma. The data illustrate the heterogeneity of the presenting clinical features of fatal pediatric melanoma and the diverse characteristics of the affected patients, precursor lesions, and histopathology. Description of the major themes identified in fatal cases allows for better characterization of aggressive melanomas in the pediatric population and may allow for future risk stratification. Furthermore, we highlight the significance of separating pediatric melanoma into CMN-associated, spitzoid, and conventional melanoma, which have distinct presentations, genetics, and clinical courses.

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