Management of Pediatric Melanoma
and Atypical Melanocytic Neoplasms
A Growing Concern

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8th Canadian Melanoma Conference
Banff, Alberta
February 22, 2014

Disclosures

• Dr. Sondak is a compensated consultant for Merck, BMS, GSK, Amgen, Provectus and Navidea

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Definitions

**Pediatric melanoma**

- Incidence of pediatric melanoma is increasing ~2.9% per year over the last 3 decades (50% from 1988 to 2007)
- ~ 450 cases of melanoma will be diagnosed in patients <21 in the US this year
  - 1-4% of all cases of melanoma
  - 1-3% of all pediatric malignancies

**Perinatal/infantile melanoma**

*IN UTERO* *BIRTH* *ONE YEAR* *PUBERTY (~10 YRS)* *18-21 YRS*

<table>
<thead>
<tr>
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*Pediatric melanoma*

**EXTREMELY RARE**
- Transplacental transmission rare
- Melanoma arising in giant pigmented nevus
- Neurocutaneous melanosis
- De novo melanoma perhaps least common of all
  These cases do not seem to be increasing in incidence


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**Childhood melanoma**

*IN UTERO* *BIRTH* *ONE YEAR* *PUBERTY (~10 YRS)* *18-21 YRS*

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*Pediatric melanoma*

- 11% of pediatric melanomas in SEER database
- Clinical and pathologically distinct from adolescent melanoma, relationship to UV exposure very unclear
- Conflicting data on survival outcomes compared to adolescent melanoma but generally considered more favorable


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**AYA melanoma**

*IN UTERO* *BIRTH* *ONE YEAR* *PUBERTY (~10 YRS)* *18-21 YRS*

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*Pediatric melanoma*

- Pediatric melanoma category rising most rapidly in incidence
- Relationship with UV exposure still controversial

Incidence rates of malignant melanoma in children and young adults (1973 to 2001)


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Tanning bed usage in the US

• 1 million times a day someone in the US uses UV radiation for skin tanning
• According to the indoor tanning industry, tanning beds are used by 30 million Americans, or about 10% of the U.S. population, each year
• Use rate among teenage girls by age:
  – 7% at age 14, 15% at age 15, 35% at age 17
  – Median number of times of use 20

Fisher & James, N Engl J Med 2010
Geller et al. Pediatrics 2002
Lazovich et al. Arch Derm 2005

Relative Incidence of Different Pediatric Melanoma Types
(Not to scale)

Fisher & James, N Engl J Med 2010
Geller et al. Pediatrics 2002
Lazovich et al. Arch Derm 2005
Challenges in understanding pediatric melanoma

• Large scale epidemiologic studies do not report fine points of treatment and outcomes
• Only five series with more than 100 cases, all single institution (e.g. Karlsson et al 1998, Aldrink et al 2009, Paradela et al 2010, Moore-Olufemi et al. 2011, Han et al. 2012)
• One international registry series (Averbook 2013)
• Diagnostically controversial melanocytic proliferations: up to 15% of cases in series that underwent central review

Reed et al. J Natl Canc Netw 2013;11:879

Pediatric melanoma Pathologic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Paradela</th>
<th>Han</th>
<th>Aldrink</th>
<th>Cordero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial spreading</td>
<td>48%</td>
<td>46%</td>
<td>49%</td>
<td>9%</td>
</tr>
<tr>
<td>Nodular</td>
<td>34%</td>
<td>22%</td>
<td>21%</td>
<td>30%</td>
</tr>
<tr>
<td>Acral/lentiginous</td>
<td>4%</td>
<td>0%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Spitz</td>
<td>0%</td>
<td>3%</td>
<td>2%</td>
<td>13%</td>
</tr>
<tr>
<td>Other/NOS/Unclassified</td>
<td>14%</td>
<td>16%</td>
<td>24%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Paradela et al. Cancer 2010;116:4334

Pediatric melanoma Clinical/pathologic characteristics

• Slight female predominance
• ~85% Caucasian, so non-whites overrepresented

Pediatric melanoma
Distinctive clinical characteristics

- Conventional ABCD's **NOT SEEN** in 60% childhood and 40% adolescent melanoma
- More frequently amelanotic (50%)
- Nodular subtype frequent (30%)
  - Verrucous or pyogenic granuloma-like
- Thicker at presentation (median 2.5 mm)


The elephant in the room

- Atypical melanocytic proliferations (AMP)
  - Atypical Spitz nevus
  - Melanocytic proliferation of uncertain biologic potential
  - Melanocytic tumor of uncertain malignant potential (MELTUMP)
  - Pigmented epithelioid melanocytoma
  - WTF??
- Expert dermatopathologists frequently disagree about whether a lesion is benign, atypical or malignant
- Because of the long natural history and the challenges of follow-up in pediatric patients, sometimes the same lesion is counted as an AMP in one series and as melanoma in another

Pediatric Melanocytic Lesions at Moffitt
Age Breakdown by Diagnosis

<table>
<thead>
<tr>
<th>Age</th>
<th>MIS</th>
<th>Invasive Melanoma</th>
<th>AMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 10</td>
<td>0</td>
<td>5 (50%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>11 to 15</td>
<td>0</td>
<td>34 (83%)</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>16 to 21</td>
<td>7 (9%)</td>
<td>69 (86%)</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>

Messina JL, unpublished data 2010
Moffitt Experience with Pediatric Melanoma

- Excluding patients with Spitz nevus and atypical melanocytic proliferation
- Characteristics correlated with
  - SLN status
  - Age groups stratified as <12 yrs, 12 – 17 yrs, 18 – <21 yrs
  - Outcome stratified by SLN status and age groups


Pediatric Melanoma

Total # of Pediatric Melanomas 126

- Negative SLNB 44
- Positive SLNB 18 (29.0%)
- No SLNB 64
- SLNB performed 62

Reasons for no SLNB:
1). Breslow thickness <1 mm: 30
2). Before 1992 (prior to SLNB): 18
3). Nodal/distant metastasis at presentation: 8
4). Patient declined: 1
5). Lost to follow-up: 1
6). Unknown: 6

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients N=126</th>
<th>SLNB performed N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Median</td>
<td>18 years</td>
<td>17 years</td>
</tr>
<tr>
<td>Age Range</td>
<td>2 – 20</td>
<td>2 – 20</td>
</tr>
<tr>
<td>Gender Male</td>
<td>53 (42.1%)</td>
<td>28 (45.2%)</td>
</tr>
<tr>
<td>Gender Female</td>
<td>73 (57.9%)</td>
<td>34 (54.8%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>119 (94.4%)</td>
<td>58 (93.5%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (3.2%)</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.6%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up Median</td>
<td>60 months</td>
<td>73 months</td>
</tr>
<tr>
<td>Follow-up Range</td>
<td>1 – 315</td>
<td>1 – 225</td>
</tr>
</tbody>
</table>
Characteristics of SLNB Patients

<table>
<thead>
<tr>
<th></th>
<th>SLNB performed</th>
<th>+SLN</th>
<th>-SLN</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+SLN N=18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-SLN N=44</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.6 mm</td>
<td>2.55 mm</td>
<td>1.30 mm</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Range</td>
<td>0.42 – 10.4</td>
<td>1.05 – 6.2</td>
<td>0.42 – 10.4</td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 yrs</td>
<td>2 (3.2%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td></td>
</tr>
<tr>
<td>12 - 17 yrs</td>
<td>32 (51.6%)</td>
<td>9 (28.1%)</td>
<td>23 (71.9%)</td>
<td></td>
</tr>
<tr>
<td>18 -&lt;21 yrs</td>
<td>28 (45.2%)</td>
<td>8 (28.6%)</td>
<td>20 (71.4%)</td>
<td></td>
</tr>
<tr>
<td>Mitotic rate, Ulceration, Regression, VGP</td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pediatric Melanoma

Recurrence-Free Survival Stratified by SLN Status

5 yr RFS: 93.7%
5 yr RFS: 59.5%
p<0.05 for +SLN vs. -SLN
+SLN significant predictor of RFS on multivariate analysis

55.6% of melanoma-related deaths in the SLNB group occurred after 5 yrs

Melanoma-Specific Survival Stratified by SLN Status

5 yr MSS: 96.8%
5 yr MSS: 77.8%
p<0.05 for +SLN vs. -SLN

55.6% of recurrences in the SLNB group occurred after 5 yrs
Recurrence

All patients*  SLNB performed
N=122  N=62

<table>
<thead>
<tr>
<th>Type of Recurrence</th>
<th>Total Recurrences</th>
<th>1st Site of Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27 (22.1%)</td>
<td>Local 3 (2.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regional 14 (11.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distant 8 (6.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown 2 (1.6%)</td>
</tr>
<tr>
<td></td>
<td>13 (21%)</td>
<td>Local 2 (3.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regional 4 (6.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distant 5 (8.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown 2 (3.2%)</td>
</tr>
</tbody>
</table>

*Excluding 4 patients who presented with stage IV distant metastatic disease

Survival

Presented as Stage IV

<table>
<thead>
<tr>
<th>Type of Survival</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>106</td>
<td>84.1%</td>
</tr>
<tr>
<td>Died of disease</td>
<td>19</td>
<td>15.1%</td>
</tr>
<tr>
<td>Died of other causes</td>
<td>1</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Stratified by Age Groups

- <12 yrs
- 12-17 yrs
- 18-20 yrs
Sentinel node biopsy for AMP

- 24 additional patients ages 4-21 underwent sentinel node biopsy for AMP 1992-2009
- In cases with multiple pathology consultations, no agreement in any case
- Positive sentinel node in 7 (29%) with multiple positive nodes in 3 cases; 1 of 6 patients undergoing CLND had additional positive nodes
- With 4.1 years median follow-up, all patients alive

Mills et al, J Cutan Pathol 2012;39:331

Developing melanoma drugs for pediatric patients

- Pegylated interferon-α2b
  - Unclear how FDA handled pediatric requirement/waiver
  - One phase II trial underway at St Jude’s*
- Vemurafenib
  - Multicenter phase I trial about to start, age 12-17
- Ipilimumab
  - NCI* phase I all solid tumors open, ages 2-20
  - Multicenter phase II melanoma trial planned, >12
  - Also open at selected other centers

Conclusions

- Despite higher incidence of nodal metastases, survival is comparable to or better than what is historically reported for adults with melanoma
- Younger children (<12 years) appear to have better survival
- Recurrences and deaths are seen beyond 5 years and long term follow-up is necessary
Pediatric melanoma patient

Presented at age 17 with axillary nodal metastasis after recurrences of an “atypical blue nevus”

Pediatric melanoma

Failure is not an option