Dysplastic nevi with positive margins: To re-excite or not to re-excite?

Caroline C. Kim, MD, Director
Assistant Professor, Department of Dermatology
Harvard Medical School
Director, Pigmented Lesion Clinic
Associate Director, Cutaneous Oncology Program
Beth Israel Deaconess Medical Center, Boston, MA

Symposium 011: Advances in Melanoma 9:00-12:00pm
Summer AAD 2018 Meeting, Chicago, IL, July 28, 2018
Disclosures

No relevant conflicts of interest

Relationships
Hoffmann-La Roche, Ltd.
Investigator, Consultant
Overview:

1. Background
2. Synopsis of current clinical challenge
3. Review of data: outcomes of dysplastic nevi with positive margins
4. Future directions
Atypical Nevi

Background:

--First described in 1978: clinicopathologic entity, which identified patients at increased risk for melanoma

• Mole larger than 5 mm
• Variegated pigmentation
• Irregular borders

Pathology features:

Architecture:
• nests bridge rete ridges
• elongated rete ridge

Cytology:
• larger, atypical cells
• larger nucleoli

Host response:
• lymphocytic infiltrate

Atypical Nevi (Dysplastic Nevi)

Background:

- Clinical term: **Atypical nevus**
- Pathologic term: **Nevus with architectural disorder**

**Dysplastic nevus**
Atypical/ Dysplastic Nevi

Significance:

Increased risk of developing MM

- General population: ~1.93% lifetime risk
- Atypical nevi: ~2-12 x risk
- Atypical Mole Syndrome:
  --10 yr cumulative risk for developing MM
  10.7% vs. 0.62% for controls


Benign nevus

Mild dysplasia

Mod dysplasia

Severe dysplasia

Melanoma
Atypical/ Dysplastic Nevi and Risk of Melanoma

• ~50-75% of melanomas arise *de novo*
• Similar rate may be observed of melanoma arising in association with dysplastic nevi (21-56%) vs. common nevi (44-79%)
• Actual transformation rate of dysplastic nevus cells into melanoma: ???

Tsao et al. *Arch Dermatol* 2003; 139(3):282-2
Atypical Nevi

When to biopsy?

--Diagnosis of atypical nevus can be made clinically

--Biopsy suspicious lesions concerning for melanoma

--Removal also option for nevi in areas difficult to monitor
Biopsy

Variable types of biopsies performed
Guidelines of care for the management of primary cutaneous melanoma

Table IV. Recommendations for biopsy

Preferred biopsy technique is narrow excisional biopsy that encompasses entire breadth of lesion with clinically negative margins to depth sufficient to ensure that lesion is not transected, which may be accomplished by elliptical or punch excision with sutures, or shave removal to depth below anticipated plane of lesion. Partial sampling (incisional biopsy) is acceptable in select clinical circumstances such as facial or acral location, low clinical suspicion or uncertainty of diagnosis, or very large lesion. Repeat biopsy is recommended if initial biopsy specimen is inadequate for diagnosis or microstaging of primary lesion.
High suspicion for melanoma: narrow excisional biopsy preferred

1-3 mm margins

2 mm margins in saucerization method: ~87% of excisional biopsies had clear pathologic margins

Partial/incisional biopsy:

- Facial or acral areas
- Very large lesions
- Low suspicion

Be aware of limitations of partial / incisional biopsy
Dysplastic nevi: after the biopsy

Pathology result:
--grading system is variable
  dysplastic vs severely DN

Mild, mod, severely DN

Mild, mild-mod, mild-focal mod, mod-focal severe, mod-severe, severe

No guidelines on indications for reexcision
Pathology interobserver variability:
Pathologists’ diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study
Elmore JG et al. BMJ. 2017 Jun 28

• Skin biopsy cases (n=240), Pathologists from 10 US states were randomized to independently interpret the same set on two occasions (phases 1 and 2), at least 8 months apart

• Diagnosed in 5 classes: I (eg, nevus or mild atypia)
  • II (eg, moderate atypia)
  • III (eg, severe atypia or melanoma in situ)
  • IV (eg, pathologic stage T1a (pT1a) early invasive melanoma)
  • V (eg, ≥pT1b invasive melanoma).

• Reproducibility was assessed by intraobserver and interobserver concordance rates
Pathology interobserver variability:
Pathologists’ diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study
Elmore JG et al. BMJ. 2017 Jun 28

- Intraobserver concordance: highest for class I 76.7% and class V 82.6%.
- However, the intraobserver reproducibility was lower for class II (35.2%), class III (59.5%), and class IV (63.2%).
- Average interobserver concordance rates were lower, but with similar trends.
- Efforts to improve clinical practice should include using a standardized classification system, acknowledging uncertainty in pathology reports, and developing tools such as molecular markers to support pathologists' visual assessments.
Management of Dysplastic Nevi with Positive Biopsy Margins: US
Atypical Nevi

Management in US: 2002

Questionnaire mailed to 1216 fellows of AAD: 456 responded

--86% of respondents intend to do total removal when performing biopsy of an atypical nevus

--75% use margins of 2mm or less

--67% prefer to re-excite dysplastic nevus when margins positive, some use histologic atypia as criterion

<table>
<thead>
<tr>
<th></th>
<th>Observe or other</th>
<th>Reexcise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2009 Chicago</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>79%</td>
<td>21%</td>
</tr>
<tr>
<td>Mod</td>
<td>19%</td>
<td>81%</td>
</tr>
<tr>
<td>Mod-Sev</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>2014 New England</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>39%</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

No consensus


Tong L, Wu P and Kim CC (JAAD 2016)
Other recent survey studies

Management Strategies of Academic Pigmented Lesion Clinic Directors in the United States.
Nelson KC et al. JAAD Jan 2018

- Survey of pigmented lesion clinic directors in U.S.; 40 directors identified, 38 responded (95%)
- Recommended management of moderate DN with + histologic margins, no clinical residual:
  No re-excision: 43%; 1-2 mm margins: 27%; 3-4 mm margins: 21%.

A Survey Analysis on the Management of Moderately Dysplastic Nevi Among Academic Dermatologists Across the United States
Tessitore et al. JAAD May 2018

- Survey emailed to 385 members of Association of Professors Dermatology
- 131 responses (34%) showed varied responses for scenarios
- Absence of visible pigment in a positive biopsy margin (lateral, deep or deep and lateral) markedly increased the percentage of respondents who chose clinical monitoring (45%, 40%, 37% respectively)
Dysplastic Nevi with Positive Biopsy Margins: Outcomes Data
<table>
<thead>
<tr>
<th>Publication</th>
<th># DN with positive margins observed or re-excised</th>
<th>Distribution of atypia</th>
<th>Duration of follow up</th>
<th>#/% recurrence (AN)</th>
<th>#/% recurrence (MM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kmetz et al. 2009</td>
<td>26 observed</td>
<td>unstated</td>
<td>6.12 years</td>
<td>unstated</td>
<td>0</td>
</tr>
<tr>
<td>Goodson et al. 2009</td>
<td>69 observed</td>
<td>Mild: 65 Moderate: 4</td>
<td>At least 2 years</td>
<td>3-4 %</td>
<td>0</td>
</tr>
<tr>
<td>Hocker et al. 2013</td>
<td>115 observed</td>
<td>Mild: 66 Moderate: 42 Severe: 7</td>
<td>17.4 years</td>
<td>unstated</td>
<td>0</td>
</tr>
<tr>
<td>Flemington et al. 2016</td>
<td>159 observed</td>
<td>Mild: 2 Mild-moderate: 9 Moderate: 52 Moderate-Severe: 55 Severe: 9</td>
<td>5.5 years</td>
<td>N/A</td>
<td>2/127 (1.5%)</td>
</tr>
<tr>
<td>Reddy et al. 2013</td>
<td>127 re-excised</td>
<td>Mild: 2 Mild-moderate: 9 Moderate: 52 Moderate-Severe: 55 Severe: 9</td>
<td>unstated</td>
<td>N/A</td>
<td>(both from mod-severe DN biopsies)</td>
</tr>
<tr>
<td>Abello-Poblete et al. 2013</td>
<td>91 re-excised</td>
<td>Mod: 75 Severe: 16</td>
<td>2-16 weeks, majority after 4 weeks</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Strazzulla et al. 2014</td>
<td>495 re-excised</td>
<td>Mild:16 Mild-moderate: 137 Moderate: 342</td>
<td>Unstated</td>
<td>0.2% upgraded from Mod to Severe</td>
<td>0</td>
</tr>
</tbody>
</table>

Total 517

Mild: 131
Mod: 47
Severe: 7
?: 26

Hiscox et al 147

Total 713

Mild: 18
Mild-Mod: 146
Mod: 469
Mod-sev: 55
Sev: 25
1 (AIMP favor early MMIS)
• **Mild + margins without pigment**  →  **Observation**
• **Moderate + margins without pigment**  →  **Observation may be reasonable, more data needed**
• **Severe + margins without pigment**  →  **Re-excision**
• **Monitor all biopsy sites for unusual regrowth**

**Pigmented Lesion Subcommittee**
**MPWG/ECOG/SWOG**
Need for large-scale data to further investigate role of observation vs. re-excision of dysplastic nevi

Pigmented Lesion Subcommittee
MPWG/ECOG/SWOG
Multi-center study
Role of Observation for Excisionally Biopsied Moderately Dysplastic Nevi with Positive Histologic Margins and Risk of Development of Future Melanoma

Caroline C. Kim, MD¹,#, Elizabeth G. Berry, MD²,³*,# and Suephy C. Chen, MD ²,³
On behalf of the Pigmented Lesion Subcommittee, Melanoma Prevention Working Group
Beth Israel Deaconess Medical Center, Boston, MA ¹, Emory University, Atlanta, GA ², Atlanta VA Health Care System, Decatur, GA ³
* egberry@emory.edu, # These authors contributed equally

Presented at the Society of Investigative Dermatology Annual Meeting 2018
Recurrent Pigmentation
Recurrent Pigmentation

- **Recurrent nevi**: tend to develop within 8 months with pigmentation confined to scar

- **Melanomas**: tend to recur more than 20 months after biopsy, in patients older than 30 years, and with pigmentation crossing into normal skin

Thank you!

Caroline C. Kim, MD, Director
Assistant Professor, Department of Dermatology
Harvard Medical School
Director, Pigmented Lesion Clinic
Associate Director, Cutaneous Oncology Program
Beth Israel Deaconess Medical Center, Boston, MA
ckim3@bidmc.harvard.edu