Updates in management of dysplastic nevi and personalizing melanoma screening

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S001-Advances in Melanoma, 9:00am-12:00pm
Disclosures

No relevant conflicts of interest
Overview:

1. Updates in management of dysplastic nevi

2. Review of clinical strategies for melanoma screening

3. Personalizing melanoma screening for patients
Atypical/Dysplastic Nevi
Atypical 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


Dysplastic nevi and risk of melanoma

- 50-80% 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: ????

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

- Incisional
- Excisional
- Shave
- Punch
- Elliptical
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

* Clear margins: no need to worry about + margin debate!
Partial/incisional biopsy:

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

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

- Clinical term: Atypical mole
- Pathologic term: nevus with architectural disorder
- Recommended atypical moles be removed in total
- Recommended 2-5 mm margins for reexcisions of DN “if needed”

No guidelines on indications for re-excision
Comparison between Chicago dermatologist study and 2014 New England dermatologists survey

<table>
<thead>
<tr>
<th></th>
<th>Observe or other</th>
<th>Reexcise</th>
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</thead>
<tbody>
<tr>
<td><strong>2009 Chicago positive margins</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 positive margins</strong></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>
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</table>

No consensus


Tong L, Wu P and Kim CC (JAAD 2016)
<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>
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</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>
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<tr>
<td>Goodson et al. 2009</td>
<td>69 observed</td>
<td>Mild: 65</td>
<td>At least 2 years</td>
<td>3-4 %</td>
<td>0</td>
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<tr>
<td>Hocker et al. 2013</td>
<td>115 observed</td>
<td>Mild: 66</td>
<td>17.4 years</td>
<td>unstated</td>
<td>0</td>
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<tr>
<td>Fleming et al. 2016</td>
<td>159 observed</td>
<td>Moderate: 42</td>
<td>5.5 years</td>
<td>0</td>
<td>1 (AIMP fav early MMIS)</td>
</tr>
<tr>
<td>Reddy et al. 2013</td>
<td>127 re-excised</td>
<td>Mild: 2</td>
<td>Unstated</td>
<td>N/A</td>
<td>2/127 (1.5%) (both from mod-severe DN biopsies)</td>
</tr>
<tr>
<td>Abello-Poblete et al. 2013</td>
<td>91 re-excised</td>
<td>Mod: 75</td>
<td>2-16 weeks</td>
<td>N/A</td>
<td>0</td>
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<tr>
<td>Strazzulla et al. 2014</td>
<td>495 re-excised</td>
<td>Mild: 16</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
Pigmented Lesion Subcommittee

MPWG/ECOG/SWOG

- 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

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Management strategies of academic pigmented lesion clinic directors in the United States


- 38 of 40 identified PLC directors responded (95%) to REDcap survey 2015-6.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>No additional procedure</th>
<th>1-2</th>
<th>3-4</th>
<th>5</th>
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<tbody>
<tr>
<td>Diagnoses with positive histologic margins and no clinical residuum, n %</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nevus with mild atypia (n = 35)</td>
<td>32 (91)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Nevus with moderate atypia (n = 33)</td>
<td>17 (43)</td>
<td>9 (27)</td>
<td>7 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Nevus with severe atypia (n = 35)</td>
<td>0</td>
<td>2 (6)</td>
<td>12 (34)</td>
<td>17 (48)</td>
</tr>
</tbody>
</table>
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
Risk of Subsequent Cutaneous Melanoma in Moderately Dysplastic Nevi Excisionally Biopsied but With Positive Histologic Margins

Caroline C. Kim, MD; Elizabeth G. Berry, MD; Michael A. Marchetti, MD; Susan M. Swetter, MD; Geoffrey Lim, MD; Douglas Grossman, MD, PhD; Clara Currie-Lewandrowski, MD; Emily Y. Chu, MD, PhD; Michael E. Ming, MD, MSCE; Kathleen Zhu, BA; Meera Brahmbhatt, MD; Vijay Balsekharan, BS; Michael J. Davis, BMus; Zachary Wolner, BA; Nathaniel Fleming, BA; Laura K. Ferris, MD, PhD; John Nguyen, BA; Oleksandr Trofimenko, BA; Yuan Liu, PhD; Suephy C. Chen, MD, MS, for the Pigmented Lesion Subcommittee, Melanoma Prevention Working Group
Objective:

- To determine outcomes and risk for the development of subsequent cutaneous melanoma from moderately dysplastic nevi that had been excisionally biopsied with positive histologic margins observed for ≥ 3 years (January 1, 1990-August 31, 2014)

Design:

- Multicenter (9 US academic dermatology sites) retrospective cohort study
- Patients ≥ 18 years of age with a moderately DN excisionally biopsied with + histology margins with ≥ 3 years of clinical f/u
- Central dermatopathology review: 5 representative slide cases were reviewed per site to confirm histologic grading

Main outcomes and measures:

- Development of melanoma at 1) the same biopsy site or 2) elsewhere on the body
Results:

467 moderately DN + margins from 438 patients with a mean f/u time of 6.9 years.

- No biopsy-site melanomas developed
- **100 patients (22.8%)** developed a cutaneous melanoma at a separate site
- Multivariable analysis revealed that **history of cutaneous melanoma** was significantly associated with the risk of subsequent melanoma at a separate site (OR 11.74; 95% CI: 5.71-24.15; p<0.001) as were 2 or more prior biopsied dysplastic nevi (OR 2.55; 95% CI, 1.23-5.28, p=0.1).

Central dermatopathology review:

- **Agreement in 35 of 40 cases (87.5%)**
- 3 of 40 cases upgraded in degree of atypia. Of these, 1 was interpreted as melanoma in situ. That patient remains without recurrence or evidence of melanoma after 5 years of follow-up.
Conclusions:

- Close observation with routine surveillance is a reasonable management approach for moderately dysplastic nevi (excisionally biopsied) with positive histologic margins.

- However, having 2 or more biopsies dysplastic nevi (1 of which is moderately dysplastic) appears to be associated with an increased risk for melanoma at a separate site—recommend continued surveillance.
Summary

Dysplastic nevi with positive biopsy margins:

• Recent outcomes data: observation of moderate dysplastic nevi that have been excisionally biopsied with + histologic margins may be reasonable; continued surveillance is important.

• Future larger scale data: other subtypes of nevi, outcomes, margin types, patient populations.

• If observing, clinician and patient should monitor biopsy sites for unusual regrowth.
Melanoma Screening: Can we personalize to optimize results?
How do we diagnose melanoma?

A. Asymmetry
B. Border irregularity
C. Color variegation
D. Diameter
E. Evolution
F. Funny looking

“Ugly duckling”
MALIGNANT MELANOMA

- Acral Lentiginous Melanoma
- Lentigo Maligna Melanoma
- Nodular melanoma
- Superficial Spreading Melanoma
- Nodular melanoma
- Lentigo Maligna Melanoma
- Acral Lentiginous Melanoma

Superficial Spreading Melanoma
Epiluminescence Microscopy

• Clinical exam alone: 65-80% melanomas correctly diagnosed

• With dermoscopy: 70-95%

Training necessary!

Without training, dermoscopy decreased rate of melanoma detection


• Mayer 1997

• Binder et al. 1997
Who is at risk for melanoma?

Risk factors:

-- Genetics:
  CDK2NA and CDK4
  Abnl p16 in 30-50% of familial melanoma
  Abnl p16 in 25-40% of sporadic melanoma

Other genetic alterations:
  BRAF, NRAS, KIT, GNAQ, GNA11, MC1R, phosphatase and tensin homologue (PTEN/MMAC1), p53, BAP1

-- Fair skin
-- UV irradiation
-- Increased numbers of nevi >50
-- Atypical nevi

-- Immunosuppression
-- Personal or FH of melanoma
-- Red hair
Patients with >50 nevi: “moley” patients
“Signature” Nevi
Atypical nevus patients
Total Body Digital Photography

-- can detect subtle changes and de novo lesions: detection of early melanoma
--can reduce the number of lesions excised
--can reduce patient anxiety

Canfield Scientific, Inc.


Total Body Digital Photography

-- can detect subtle changes and de novo lesions: detection of early melanoma

--can reduce the number of lesions excised

• Reviewed records of all patients in 2 pigmented lesion clinics who received TBP and had 2 or more f/u visits over at least 2 years.
• Before PLC/TBP vs. after PLC/TBP:
  -- mean rate of biopsies: 1.62 vs. 0.34 per year.
  -- 3.8-fold reduction in nevus biopsies

Retrospective chart review of 281 melanoma patients seen over 1 year at BIDMC, Harvard Medical School, Boston

- 89 patients with >50 moles (HNC), 192 with <50 moles (LNC)

- Compared pts with >50 moles, pts with <50 moles:
  - were diagnosed at older age (51 years vs. 41 years, p<.001)
  - had thicker tumors (1.8 mm vs. 1.3 mm Breslow depth, p < 0.01)
  - tumors had a higher average mitotic rate (4 mits/mm2 vs. 2 mits/mm2, p=.05)
  - tumors more likely to be nodular subtype vs. superficial spreading, (p< .05)

- Those with <50 moles had more aggressive tumors
Patients with no nevi, many lentigines
Patients with red hair phenotype/pink moles
Cross-sectional, retrospective chart review of 933 melanoma patients with known presenting tumor color identified (342 with amelanotic melanoma (AMM) vs. 591 with pigmented melanoma (PMM)).

Compared to pigmented melanoma, amelanotic melanoma was associated with:
--- older age at diagnosis (51 years vs. 41 years, p<.001)
--- history of nonmelanoma skin cancer (1.8 mm vs. 1.3 mm Breslow depth, p < 0.01)
--- red hair
--- head and neck location
--- more aggressive pathology
--- less likely associated with a precursor nevus

Amelanotic melanoma was inversely associated with:
--- FH of melanoma
--- >50 nevi
--- history of DN

Amelanotic melanomas were:

--more likely to be misdiagnosed than patients with PMM (25% vs. 12% clinically, and 12% vs. 7% pathologically

--poorer melanoma-specific survival  (5-year overall survival rate , 0.77 [95% confidence interval, 0.72-0.82] vs. 0.84 [95% confidence interval, 0.80-0.87])
Patients with a prior melanoma
Second primary melanomas

Vernali et al. Association of incident amelanotic melanoma with phenotypic characteristics, MC1R status and prior amelanotic melanoma. JAMA Dermatology (published online July 26, 2017).

- 24 patients with amelanotic melanoma: 20.8% had prior amelanotic melanoma
- 503 patients with pigmented melanoma: 5.4% had prior amelanotic melanoma

Patients with amelanotic melanoma more likely to have a prior amelanotic melanoma (OR 4.62; 95% CI, 1.25-14.13, p=0.01)

However:
- Second primary melanomas may not look like the first melanoma!
- Educate patients: continue looking for any ugly ducklings
Thank you!

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