Dysplastic Nevi: How to Manage?

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

David Polsky MD, PhD
S004 Advances in Melanoma

DISCLOSURES

DermTech Int’l – former Advisory Board and Consultant
MoleSafe, USA - Provider of diagnostic services utilizing dermoscopy
Overview

• Clinical significance of dysplastic nevi
  – Potential melanoma precursors?
  – Markers of increased patient risk for developing melanoma?
  – Clinical simulators of melanoma

• How can we manage:
  – Patients with dysplastic nevi
  – Individual dysplastic nevi
    • Clinical diagnosis
    • Biopsy method
What are dysplastic nevi?

• In 1978 papers by Clark and Lynch described atypical moles in melanoma-prone families
  – ‘Large moles of variable size and color with pigmentary leakage’ – Lynch
  – Histologic appearance characterized by Clark
• Documentation of melanomas arising in association with these moles
• High-risk phenotypes named (Dysplastic Nevus Syndrome, Familial Atypical Mole and Melanoma Syndrome)
• Subsequent reports suggested that histologic dysplasia was sufficient to diagnose the syndrome
Initial descriptions of dysplastic nevi profoundly affected clinical practice

- Few examples of melanomas arising in association with dysplastic nevi suggested that dysplastic nevi are melanoma precursors

- **Histopathologic diagnosis** was needed to identify patients at increased risk for melanoma

- These concepts support the practice of:
  - Biopsying dysplastic nevi even if you don’t think it’s melanoma – “Dx: rule out dysplastic nevus” – to assign melanoma disease risk to the patient or catch the melanoma before it develops
  - Telling patients they have “pre-melanoma” if a biopsied nevus has histologic dysplasia
Dysplastic nevi are rarely melanoma precursors

- Clinically atypical nevi are very stable
  - Clark, 1978 - “Serial photographs … taken during periods of 2-5 years showed no evidence of growth”
  - Naeyaert JM - 1 in 10,000 Dysplastic Nevi/year develop associated melanoma
  - Tucker – Longitudinal follow up of 884 patients from melanoma-prone families (range 2 yrs – 25 yrs)

  - “The majority of dysplastic nevi either remain stable or regress; few change in a manner that should cause concern for melanoma. With careful surveillance, melanomas can be found early.”

  - 108 melanomas diagnosed during the study

Markers of increased patient risk for developing melanoma?

Yes, but we don’t need to biopsy them to determine the patient’s risk
Multiple studies support the role of atypical nevi as risk factors for melanoma

**Number of moles and clinically recognized atypical moles are melanoma risk factors**

- Tucker MA (1997) JAMA
  - Large melanoma case-control study (n~1700)
  - All nevi >2mm were counted and categorized by size and appearance
    - Dysplastic nevi defined as having a flat portion plus haphazard color, indistinct or irregular borders, asymmetry
  - Melanoma risk increases with increasing numbers of nevi
    - Relative risk ranged from 1.8 – 3.4
  - Melanoma risk increases with increased number of clinically atypical nevi >5mm in diameter
    - Relative risk ranged from 2.3 – 12 for patients with between 1 and ≥10 large atypical nevi
Histologic dysplasia of a nevus is associated with a patient’s total number of nevi

- Roush and Barnhill (1991)
  - 150 melanoma patients with dysplastic nevi
  - Biopsy the most clinically atypical lesion
  - Correlated clinical and histological features
  - Results:
    - Histological dysplasia was significantly correlated with total number of nevi, not their clinical appearance

Roush & Barnhill (1991) *Br J Cancer, 64*:943-7
Dysplastic nevi as melanoma simulators

“B-K Moles”
Back of 27-year-old woman who had four primary melanomas
Clark WH, Arch Dermatol (1978) 114:732

All 4 lesions are histopath dx’d as dysplastic nevi
Options in managing melanoma simulants

- Remove all clinically atypical nevi to prevent melanoma?
- Biopsy the most atypical looking lesion at each visit?
- Use tools to improve diagnostic accuracy
- Example tools:
  - Total Body Photography
  - Dermoscopy
  - Serial dermoscopic monitoring
  - Confocal microscopy
  - Computer-aided diagnostic devices (i.e. Melafind)
  - Non-invasive gene expression ‘patch biopsy’ (i.e. DermTech PLA assay)
Total Body Photography

• 26 images of the cutaneous surface taken at a precise distance from the patient using optimized lighting

• Patients are compared to their photographs at subsequent visits

• Photographs are not generally obtained until adulthood and not repeated

Total Body photography can reduce nevus biopsies and enhance melanoma detection

- **Reducing nevus biopsies**
  - Data from Salt Lake City and Boston pigmented lesion clinics (n=589 high risk patients)
    - TBPs reduced biopsy rate from 5.92 to 1.56 biopsies/patient

- **Enhancing melanoma detection**
  - Data from MSKCC (n=576 patients, 27 melanomas diagnosed, 21/27 in-situ)
    - 74% of melanomas biopsied because of changes and 19% because they were new lesions
    - 30% of melanomas were discovered by the patient using self examination
    - 26% of lesions of concern to patients did not require biopsy

Dermoscopy takes surveillance to the next level
Benefits of Dermoscopy

- Increase in diagnostic accuracy
  - Meta-analysis of 9 studies performed in clinical settings
  - Odds Ratio = 15.6 for melanoma diagnosis via dermoscopy vs. naked-eye examination
- Decrease in the benign-to-malignant ratio
  - Decrease 20:1 to 5:1 for pigmented lesion specialists and general dermatologists
- Decrease in unnecessary excisions
- Increase in clinical diagnostic confidence
- Caveats: Requires training

Simple and Not-so-Simple Patterns in Dermoscopy
Knowing simple patterns can reduce nevus removals

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**NYU Langone Medical Center**

![Picture](image)

How did he do it?

“If I couldn’t describe easily, I biopsied it”

Limitations of Dermoscopy

• “Featureless melanomas”
  – Early melanomas that lack dermoscopic features of melanoma
  – Recognition of these melanomas can be enhanced using sequential dermoscopic imaging
    • Melanomas are more dynamic than nevi
    • Lesion change can be observed dermoscopically

Prospective validation of short-term monitoring

- Menzies et al. 2009 Br J Dermatol
  - Trained 63 primary care physicians in dermoscopic monitoring
  - 374 lesions clinically assessed and initially selected for excision
  - Using short-term monitoring
    - Only 163 lesions were excised
    - Decrease of 209 lesions (56%)
  - 42 lesions were malignant (34 melanoma, 8 NMSC)
  - Benign : Malignant ratio decreased from 9.5 : 1 to 3.5 : 1 (p<0.0005)
  - Sensitivity to detect melanoma was 97.1%

Menzies et al. *British Journal of Dermatology (2009)*161:1270
Getting started with sequential dermoscopic imaging

- Especially useful for patients with multiple nevi, especially clinically atypical nevi

- Follow up strategy:
  - Initial follow-up = 3 months to maximize compliance
  - Longer term monitoring to avoid missing slower growing melanomas

- Photodermoscopy Equipment

What about teledermoscopy?

- Telemedicine/Teledermoscopy
  - Store-and-forward dermoscopic images for expert review
  - Similar or greater diagnostic accuracy than face-to-face consultations in several studies from different centers
  - Mobile phone teledermoscopy is being tested for feasibility in small studies

- MoleMap NZ commercialized >20 years in New Zealand, >6 years Australia and USA (MoleSafe)

- In New Zealand - 200 melanomas per year; 48% in-situ/52% invasive
  - 67% of invasive cases <0.75 mm in thickness

- Benign-to-malignant ratio = 3:1, decreased from 7:1 as dermoscopists gained experience with the system

- Sensitivity for melanoma = 98% based on published study (n=200 patients; 491 lesions)

The MoleSafe System

- Combines Total Body photography with dermoscopy of atypical skin lesions
- Trained nurse “Melanographers” perform skin exams and image patients
  - Low threshold for dermoscopic imaging of atypical lesions
- Dermoscopy-trained Dermatologists review all images and complete the diagnosis using a secure internet telemedicine application
- MoleSafe reports and follow up instructions sent to patient and referring MD
What about other tools?
<table>
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<tr>
<th>Confocal Microscopy</th>
<th>Melafind</th>
<th>DermTech Pigmented Lesion Assay (PLA)</th>
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<tbody>
<tr>
<td>• High sensitivity and specificity</td>
<td>• FDA approved, high sensitivity; low specificity</td>
<td>• Adhesive tapes (x4) harvest RNA from stratum corneum</td>
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<tr>
<td>• Requires high-level expertise; used mostly in specialized centers</td>
<td>• ?additive value in the evaluation of atypical lesions</td>
<td>• RNA gene expression score for 2 genes</td>
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<tr>
<td>• New reimbursement coding available</td>
<td>• Post-approval, real-world use studies needed</td>
<td>• Sensitivity = 98% -- Specificity = 73%</td>
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<td></td>
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<td>• Additional larger validation studies pending</td>
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<td>• Concerns over assay failure rate being addressed</td>
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Pellacani JAAD (2005); Guitera JID (2010); FDA PMA P090012 Executive Summary November 18, 2010; Gerami JAAD (2014) 71:237
You decide to biopsy a clinically atypical nevus –

Does it matter how you biopsy it?
Assuming you removed the entire lesion clinically, and the diagnosis was dysplastic nevus
What do you do next?

**MONITOR the biopsy site,**
**or Re-EXCISE**
Histologic atypia and margin status determine re-excisions of dysplastic nevus biopsy sites

Recent consensus statement Feb 2015
Melanoma Prevention Working Group

• Review of studies that examined outcomes of atypical nevi biopsied with positive margins
  – Limitations: No prospective trials, some studies underpowered

• Specific recommendations:
  – Clear margins:
    • mildly and moderately atypical nevi do not need re-excision
    • no comment on severely atypical nevi
  – Positive margins without clinical residual pigmentation:
    • mildly atypical nevi can be observed
    • moderately atypical nevi can also be observed (but need more data)
    • severely atypical nevi should be re-excised

Problem: Inconsistent grading of atypia can compromise this approach

- Agreement between dermatopathologists regarding the degree of atypia in dysplastic nevi is low, ranging between 16% to 65%

- Studies using pre-defined criteria have shown higher degrees of agreement

- Such standards, however, are not commonly applied in practice

- One dermatopathologist’s moderate atypia may be another’s mild atypia

- Cautious practitioners are likely to continue to re-excise dysplastic nevi with moderate atypia until more definitive data become available

Can we prevent these potentially unnecessary procedures?

Are we wasting $$$ and increasing patient morbidity so that we can sleep better at night?

Is the practice of re-excising biopsy proven DN warranted?
1) At the time of initial biopsy remove the entire lesion with an adequate margin;

2) Thoroughly examine the margin;

3) If it’s clear, we’re done! - “One and Done”
Prospective, multi-investigator study of 2-mm margins for the biopsy of clinically atypical/dysplastic nevi (CAN/DN)

Aim: To evaluate the efficacy of a standardized saucerization biopsy to completely remove CAN/DN.

In the pathology lab, all study lesions are bisected and entirely step-sectioned to assess margins thoroughly.

Images courtesy of Shane Meehan, MD.
Result: 2mm margin cleared 87% of dysplastic nevi

- 151 clinically atypical pigmented lesions biopsied
- 137 melanocytic in origin
- 78 Dysplastic Nevi evaluable (5% severe atypia)
- 68/78 (87%) removed with clear margins
  - 95% confidence interval (78% - 93%)

Terushkin, Ng, Stein, Katz, Cohen, Meehan, Polsky (manuscript in preparation)
What about scarring, other considerations?

• Patient selection
  – Level of concern regarding scarring
  – Anatomic site
  – Co-morbidities (e.g. anti-coagulation therapy)

• If saucerization is not desired, excise with a 2mm margin!

• An 8mm punch will remove a 4mm lesion with a 2mm safety margin
Potential Implications

• Reducing the number of cases with positive margins can:
  – Reduce morbidity by reducing the number of second procedures
  – Potentially reduce healthcare costs

Summary

- Patients with large numbers of nevi are likely to have histopathologically dysplastic nevi.
- Number of nevi and the presence of clinically atypia identify patients at increased risk of melanoma.
- Don’t biopsy clinically atypical/dysplastic nevi to rule out dysplastic nevus.
- Do biopsy clinically atypical/dysplastic nevi if you cannot confidently exclude melanoma.
- Use tools to increase your diagnostic accuracy.
- When removing dysplastic nevi, remove the entire lesion with a 2mm margin.
Questions, Comments?

Thank you