The State of the Dysplastic Nevus in the 21st Century

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Disclosures

• Myriad Genetics
  – Advisory board; honorarium
• Castle Biosciences
  – Advisory board; honorarium

What do I do?

• Clinical
  – 60% Mohs micrographic and reconstructive surgery and high risk skin cancer
  – 40% Dermatopathology sign-out
  – Multidisciplinary cutaneous oncology program – Huntsman Cancer Institute
• Administrative
  – Residency Program Director, Dermatology
The current(ish) state of affairs…

Do you believe dysplastic (Clark) nevi are truly premalignant lesions?
A. Yes
B. No
C. Unsure

25% 53% 22%
How do you report “dysplastic nevi”?

A. Dysplastic nevus  
B. Clark nevus  
C. Nevus with architectural disorder  
D. Other

- 62%  
- 7%  
- 19%  
- 12%

Do you assign a histologic “grade” to these nevi?

A. Yes  
B. No

- 87%  
- 13%

If yes, what grading system do you use?

A. Cytology as three grades (mild, moderate, severe)  
B. Cytology and architecture as two separate grades  
C. Cytology as two grades only  
D. Other grading system

- 73%  
- 8%  
- 10%  
- 10%
Origin of Familial Malignant Melanomas
From Heritable Melanocytic Lesions

"The B-K Mole Syndrome"

Melvin E. Clark, Jr., MD; Ronald R. Simon, MD; Mark Greer, MD; Lee R. Arentz, MD; Richard I. Mermayn, MD

Arch Dermatol 116:732-735, 1979

Journal of Medical Genetics, 1978, 16, 312-316

Familial atypical multiple mole-melanoma syndrome

HENRY T. LYNCH, BERT C. FRICHOT, III, AND JANE F. LYNCH

From the Department of Preventive Medicine/Public Health, Creighton University, Omaha, Nebraska; and the Department of Dermatology and Preventive Medicine/Public Health, Creighton and Nebraska University Health Foundation, Omaha Veterans Administration Hospital, Omaha, Nebraska, USA

SUMMARY A family is described showing concordance for malignant melanoma and a cutaneous phenotype characterized by multiple large moles of variable size and colour (reddish-brown to bluish red) with pigmented leakage. Transmission of the cutaneous phenotype in the subject family, and in several others currently under investigation, shows an inheritance pattern consistent with a simple autosomal dominant factor. This cutaneous phenotype signifying melanoma risk may now be added to an increasing body of knowledge dealing with cancer-related dermatomes.

Brief history

• 1978 – Dr. Clark describes nevi associated with melanoma prone families
  – The B-K mole syndrome
• 1978 – Dr. Lynch describes a single multi-generational family with melanoma and nevi
Brief history

• 1980 – Dr. Elder and Clark describe ‘dysplastic nevi’ in a non-familial setting
  – Introduction of the term ‘dysplastic nevus syndrome’
    • Familial and sporadic variants
    • Formally postulated that ‘dysplastic nevi’ are precursors of melanoma

The concept evolved…

Dr. Wallace H. Clark, Jr.

Dr. David Elder
When you are frustrated by the pathology report and management of these lesions please send all complaints to…

**Review**

**Dysplastic nevus: Fact and fiction**

Crist O. Rosenbluth, MD, PhD, John M. Greenfield, MD, and Syed Asaad T. Qazi, MD

Department of Dermatology

J Am Acad Dermatol 2015;73:513-4

The term “dysplastic nevus” (DNC) implies that this nevus entity is a distinct and defined entity of premalignant nature. In 2013, we evaluated the current state of knowledge and found several entities that are histologically and possibly genetically different from common nevi. Studies show that melanoma associated with a “dysplastic” nevus is just as likely to arise as a common nevus as in DNs. Furthermore, there is no evidence that a histologically defined DNC evolves into a melanoma or that the presence of 5 or more DNs in an individual patient elevates any increased melanoma risk. We suggest that the term “dysplastic nevus” be abandoned so that the focus can shift to confirmed and relevant indicators of melanoma risk, including high nevus counts and large nevus size. J Am Acad Dermatol 2015;73:513-4.

- Recommend abandoning the term “dysplastic nevus.”
- Highlights melanoma risk is linked to high nevus counts and large nevus size

**Points/Counterpoint**

**Point: What’s in a name?**

David E. Ellis, MD, MS, PhD, FACP, Philadelphia, Pennsylvania

J Am Acad Dermatol 2015;73:513-4

**Counterpoint: The “dysplastic” nevus**

What I do and do not believe

Chie J. Cockerell, MD


**Key words:** dysplastic nevus, epidemiology, melanoma, nevus risk.
Dysplastic nevi are benign neoplasms of melanocytes that are significant in relation to melanoma in 3 ways: as potential precursors, markers of increased risk, and simulants.

Dysplastic nevi are intermediate between common nevi and melanoma – clinically, microscopically and genomically.

...in my opinion the term “mild dysplasia” should be abandoned.

I believe that most so-called ‘severely dysplastic’ are either melanoma or melanoma in situ arising in a nevus.

I believe it would be reasonable to change the name ‘dysplastic’ nevus.

I do not believe the name ‘dysplastic’ nevus will change anytime soon.

What is a dysplastic nevus?
Table II. Histologic criteria proposed by Clark et al.¹⁰

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Nests bridge rete&lt;br&gt;Nests at the side of rete&lt;br&gt;Single cells between nests, nests predominating&lt;br&gt;Leptinoid elongation of rete&lt;br&gt;Anastomosis of rete&lt;br&gt;Little or no pagetoid spread</td>
</tr>
<tr>
<td>Host response</td>
<td>Patchy lymphocytic infiltrate&lt;br&gt;Epithelioid fibroplasia&lt;br&gt;Lamellar fibroplasia&lt;br&gt;Prominent vessels</td>
</tr>
<tr>
<td>Cytology</td>
<td>Variable slight to moderate atypia&lt;br&gt;Few (if any) mitoses&lt;br&gt;Occasional macronuclei&lt;br&gt;Scattered epithelioid nevus cells&lt;br&gt;Scattered cells with finely granular melanin</td>
</tr>
</tbody>
</table>

Table III. World Health Organization criteria for the diagnosis of dysplastic nevi¹²

| Major criteria*  | Basilar proliferation of atypical melanocytes, extending at least three nests ridges beyond dermal component<br>Organization of proliferation in lentiginous or epithelioid cell pattern |
| Minor criteria*  | Lamellar or concentric eosinophilic fibrosis<br>Neovascularization<br>Inflammatory response<br>Fusion of rete ridges |

*The diagnosis of dysplastic nevus requires fulfillment of both major criteria and 2 minor criteria.
Table IV. European Organisation for Research and Treatment of Cancer Cooperative Group criteria

<table>
<thead>
<tr>
<th>Common nevus</th>
<th>Dysplastic nevus</th>
<th>Melanoma in situ</th>
</tr>
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<tbody>
<tr>
<td>&lt;2 features noted below</td>
<td>≥3 of the following features: marked junctional proliferation, irregular nevus nests, large nuclei, and lymphohistiocytic infiltrate</td>
<td>Pagetoid growth Continuous junctional proliferation</td>
</tr>
</tbody>
</table>

Shea CR, Vollmer RT, Prieto VG, Correlating architectural disorder and cytologic atypia in Clark (dysplastic) melanocytic nevi, Hum Pathol 1999, 30:500-5

"I know one when I see one."

Duncan et al., J Invest Dermatol 1993, 100:318S-321S
Weinstein et al., Arch Dermatol 1997, 133:953-958
Clemente et al., 1991 Hum Pathol 22:313-319
Figure S34. Case 35.

A.

E.

p16 (HP)
Mutations in nevi

- Common nevi have a high rate of BRAF V600E mutations
- Sporadic dysplastic nevi appear to be enriched for NRAS and BRAF non-V600E mutations
- Recurrent TERT promoter mutations in a significant portion of dysplastic nevi
Myriad myPath™ Melanoma Score: -0.6

Myriad myPath™ Melanoma allows a molecular signature measured by qRT-PCR that quantitatively a sample as malignant, benign or indeterminate. This graph shows your patient’s score relative to Myriad myPath™ Melanoma Boxes according to the range of benign and malignant lesions in the independent validation cohort with a threshold of "0."

- For Boxes from 0-0.2 the gene expression is benign, for Boxes from 0.3 to 0.6 the gene expression is indeterminate, and for Boxes with a malignant gene expression score above 0.7.
- Boxes outside of the malignant range may lead to further consultation or follow up with the ordering physician.

What do we do now?
Clinical decision making based on histopathologic grading and margin status of dysplastic nevi

Keith L. Duffy, MD;* David J. Mann, MD;* Venna Ferconi-Rosic, MD;* and Christopher R. Sheu, MD;* Salt Lake City, Utah and Chicago, IL.
The decision to re-excite moderately dysplastic nevi inverted from a minority (9%) to a majority (81%) as a function of positive margin status.

Results

- 467 moderately dysplastic nevi with positive histologic margins observed for >3 years
  - Median f/u 6.9 years
- **NO** cases of cutaneous melanoma developed at those sites
- 100 patients (22.8%) developed a cutaneous melanoma at a separate site
Do you think there is a TERT promoter mutation in this lesion?

Dx: Compound dysplastic nevus with moderate cytological atypia, narrowly excised 100x

49 year old, left lower back
40x
A nongrading histologic approach to Clark (dysplastic) nevi: A potential to decrease the excision rate

Danet E Lucey, MD, Michael J. Zipper, MD, and Jason B. Lee, MD
Philadelphia, Pennsylvania

Study results

- 17,024 Total nevi
- 8654 cases Clark nevi (50.8%)
- 959 recommended for re-excision (11.1%)
- 765 re-excised (79.8%)
Study results

• Of those re-excised 765
  – 621 no residual nevus (81.2%)
  – 123 identifiable benign component (16.1%)
  – 6 not classifiable as benign or malignant
  – 15 melanoma (2.0%)
    • 12 MIS
    • 3 superficially invasive

My dermatopathologic approach?

• Less use of the term dysplastic nevus, Clark’s nevus or nevus with architectural disorder
  – Use of the terms ‘junctional or compound lentiginous nevus’
  – Atypical junctional/compound melanocytic proliferation

How do I practice?

• I **never** diagnose a lesion with moderate or severe dysplasia
• In my estimate this is unfair to the clinician
How do I practice?

• Make specific recommendations to the clinician on management of the lesion

Report example

2 - COMPOUND MELANOCYTIC PROLIFERATION WITH ATYPICAL FEATURES [SEE COMMENT]

COMMENT: The overall features appear to be most consistent with a compound dysplastic nevus; however the asymmetry of the proliferation, scattered atypical melanocytes and rare melanocytes above the dermo-epidermal junction are unusual features. A complete re-excision is recommended given the lateral margin involvement.

My colleagues in dermatopathology, Drs. Scott Farrell and Annell Bowen, have also reviewed this case and they agree with the above interpretation.

Keith Duffy, MD
Dermatopathologist
University Hospital 8/12/2015 8:17:04 AM

Always another set of eyes…
Conclusions

- Dysplastic nevi appear to be different histologically and genomically
- Still...only a small number progress to melanoma
  - Which ones?
  - Will the genomic and personalized medicine revolution make our job better/easier/more conclusive?

Conclusions

- We are still stuck in The (seemingly) Eternal Debate
- Pigmented lesions are a team sport
  - Clinician concern
  - Consensus dermatopathology opinion
  - Photographs!
- Molecular medicine is coming commercially to a lab near you
Thank you. Questions or comments? Keith.duffy@hsc.utah.edu