Dysplastic Nevi
An Update

Ibrahim Khalifeh, M.D.
Outline

• History of Dysplastic Nevi (DN)
• Epidemiology of DN
• DN and Melanoma risk
• Current definitions of DN
• Histology of DN
• Molecular classification
• Treatment of DN
Introduction

• Controversy and confusion
  – Nomenclature
    • B-K mole
    • Atypical nevus
    • Clark’s nevus
    • Dysplastic nevus
    • Nevus with architectural disorder (NAD)
  – Diagnosis
    • Clinical and histological
  – Relation to malignant melanoma
  – Treatment
History of Dysplastic Nevi (DN)
History - B-K mole syndrome

Origin of Familial Malignant Melanomas From Heritable Melanocytic Lesions.

- Unique moles appearing in patients with familial melanoma
- Combination of unique clinical and histological features defined the “B-K mole syndrome”
History - B-K mole syndrome

• Thought to represent precursor lesions to melanoma
  – Photographic documentation of progression to MM in two cases

• 17 patients with MM

• 41 non-melanoma relatives examined

History - B-K mole syndrome

- Of the 17 persons with melanoma and a biopsied mole, 15 had the syndrome
  - Only 15 were biopsied (therefore all biopsied had the syndrome)
  - Definitionally the mole can only be identified histologically per the paper
- Of the 41 non-melanoma family members, 22 were biopsied
  - 22 had the syndrome

History - B-K mole syndrome

- Affected patient may have <10 or >100 moles
  - Every cutaneous surface, scalp to feet
  - Most prominent on trunk
  - Prototypic B-K mole is ~10mm in diameter, irregular in outline, haphazard mixture of tan, brown, black, and pink
  - Striking variability from one mole to the next

- Patients with B-K mole syndrome thought to be at “extremely high risk for development of MM”

History - B-K mole syndrome

• **Histological definition**
  – Compound melanocytic nevus
  – Atypical melanocytic hyperplasia
    • Melanocytic dysplasia – “individual melanocytes or small clusters of melanocytes that have some of the structural features of malignant melanocytes”
    • Atypical melanocytes tend to be isolated in the basilar epidermal area or disposed in nests
    • Atypical melanocytes may also be seen in the upper part of the papillary dermis

History - B-K mole syndrome

- **Histological definition**
  - Atypical melanocytic hyperplasia
    - Individual melanocytes: large and pale, spindled or epithelioid
    - Cytoplasm: abundant and filled with fine, “dusty” melanin granules
    - Mitotic figures may be identified
  - Mesenchymal changes
    - Papillary dermis is widened due to fibroplasia and new blood vessel formation
  - Lymphocytic infiltrate

Dysplastic Nevus Syndrome: A Phenotypic Association of Sporadic Cutaneous Melanoma


- First description of dysplastic nevi in patients with non-familial MM (79 patients)
- “…behave as formal histogenetic precursors of melanoma.”
- B-K mole syndrome becomes DNS sporadic and familial types
- Syndrome patients may display as few as 1 DN
The Dysplastic Nevus Syndrome: Our definition


- **DN are not “obligatory” precursors of MM**
  - 400 members of 14 melanoma prone families
  - 111 had DN & 67 had melanoma
  - **Intermediate** between common nevi and MM (clinically and histopathologically)
  - **22-36%** of sporadic MM arise in DN
  - Presence of DN in familial melanoma families defines those kindred at increased risk of developing MM
Epidemiology of DN
Epidemiology

- 5-53% of US population
  - Differences in criteria
  - Clinical criteria – 7-18%
  - Histologic criteria – 7-32%
  - Pts with history of MM – 34-59%

- Sporadic
- Familial

  Marker of increased melanoma risk

- May occur at any age
  - Familial forms – end of 2\textsuperscript{nd} decade
  - 6\textsuperscript{th} decade
  - Congenital
Dysplastic Nevi and Melanoma Risk
Dysplastic Nevi and Melanoma risk

• Many studies suggest that relationship to melanoma is related to
  – Numbers of ordinary nevi (>50 or 100)
  – Presence and number of atypical nevi as defined by
    • Size
    • Irregular or ill-defined borders
    • Variation in color
    • Macular component
Dysplastic Nevi and Melanoma risk

• Familial melanoma
  – 148-fold increased risk with DN and no previous history of MM
  – 500-fold increased risk with DN and history of MM

• Sporadic
  – 7-fold increase with DN and no personal/family history of MM

Dysplastic Nevi and Melanoma risk

- Risk of MM in persons with DN increases with increasing numbers of nevi and presence of personal or family history of MM
  - Personal hx of MM – 100x
  - At least 2 family members with MM – 200x
  - Both personal and family hx of MM – 1200x

Dysplastic Nevi and Melanoma risk

- Estimated that 1 in 10,000 DN per year will progress to MM
- Increased risk of melanoma in patients with DN not necessarily decreased with mole removal
  - MM may develop in area other than DN
- Age-adjusted incidence of MM ~15x higher in patients with DN compared to general population

Naeyaert JM, Brochez L. NEJM. Dec, 2003
Dysplastic Nevi and Melanoma risk

- Case-control study
  - 80 patients with newly diagnosed MM
  - 80 spouse controls
- The most clinically atypical nevus was biopsied
- Increased risk of MM in patients with DN having moderate to severe histological dysplasia
- Interobserver reliability with grading dysplasia was poor

**Dysplastic Nevi and Melanoma risk**

- **Retrospective analysis**
  - 1606 patients with MM

- **26.2%** of MM have associated nevi
  - DN or “other”
  - 43% DN
  - 57% other

- Younger age, SS type, truncal location correlated with associated MM and nevi

- **Most MM arise de novo**

Dysplastic Nevi and Melanoma risk

- 6,275 were diagnosed as NAD.
  - mild (2,504)
  - moderate (1,657)
  - severe (320)
- Architectural and cytological features correlate with each other
- History of melanoma:
  - 5.7% of patients with mild
  - 8.1% with moderate
  - 19.7% with severe atypia
- These data show that the probability of having personal history of melanoma, for any given NAD patient, correlates with the NAD grade.

Arumi-Uria M, et. al., Mod Pathol. 2003 Aug;16(8):764-71
Dysplastic Nevi and Melanoma risk

NIH Consensus Conference. *JAMA*. Sept, 1992

- Nevus with architectural disorder – NAD
- Margin status reported upon
- Re-excision margins of 0.2 to 0.5 mm are adequate if required
- Clinical significance of NAD should be evaluated separately in each case
- Increased relative risk for patient with non-familial atypical moles to develop melanoma ranges from 2 to 8
Dysplastic Nevi and Melanoma risk

NIH Consensus Conference. *JAMA*. Sept, 1992

- Correlation between clinical impression of atypical nevi and histology is variable
- Relationship between dysplastic nevi and increased melanoma risk is not concrete
- Difficult to establish dysplastic nevi therefore as a clinicopathological entity
Dysplastic Nevi and Melanoma risk

• Currently melanoma risk of patients is clinically established via
  – Total number of nevi
  – Presence and number of atypical nevi
  – Personal / family history of melanoma
Current definitions –
Dysplastic nevus
Current definitions – Dysplastic nevus

- May occur on any cutaneous or mucosal surface – scalp, trunk, covered areas
- 3-15 mm
- Irregular / ill-defined borders
- Asymmetrical
- Variable coloration
- Macular +/- papule
- DDx: MM, other nevi, pigmented SK, lentigo, pigmented AK, pigmented Bowen’s, and BCC
Current definitions – Dysplastic nevus

– Nevi with atypical clinical features
– Nevi with abnormal histopathological features
– Nevi with both abnormal clinical and histopathological features
– Nevi with histopathological features that are equivocal or of unknown significance

*Dermatology. Mosby, 2003.*
Current definitions – Dysplastic Nevus Syndrome

- Triad
  - ≥100 nevi
  - At least 1 nevus 8 mm or larger
  - At least 1 nevus with clinically atypical features
Histology of Dysplastic nevus
Histology

- Scanning (20x) magnification
  - Shoulder
  - Stromal response with fibrosis and inflammation

Shea CR. *Hum Pathol.* 1999 May;30(5):500-5
Histology

• Architectural disorder:
  – Circumscription: Junctional component nested at both edges vs. single-cell in at least one edge
  – Symmetrical: Good overall symmetry regarding edges, size of junctional nests, and stromal response
  – Cohesiveness of nests: >50% of nests cohesive
  – Pagetoid spread: prominent, at periphery
  – Confluent growth: in >50% of the junctional melanocytic proliferation, either as bridging of melanocytic nests or as contiguous single cells
  – Single cell proliferation: Junctional melanocytes arranged as single cells in more than 20% of the lesion

• Sum
  – Mild: 0-1
  – Moderate: 2-3
  – Severe: 4-6

Shea CR. Hum Pathol. 1999 May;30(5):500-5
Histology

• Cytologic atypia
  – Nuclear shape and staining round-oval & euchromatic
  – Nuclear size > basal-layer keratinocyte nuclei
  – Nucleoli prominent > 50% of cells
  – Cell diameter >2x basal-layer keratinocyte nuclei

• Sum
  – Mild: 0-1
  – Moderate: 2
  – Severe: 3-4

Shea CR. Hum Pathol. 1999 May;30(5):500-5
Molecular Classification
Molecular Classification

- Comparative genomic hybridization (CGH)
- DNA microarray-derived gene expression
Treatment of Dysplastic nevus
Treatment

- Assessment in conjunction with clinical history
- Observation – serial photographs
- Removal
  - Shave
  - Punch, ellipse
- Margins
  - 2 mm
  - 5 mm
- Re-excision
  - Severely atypical
  - Lack of consensus
Treatment

- Prophylactic removal – “de-moling”
- Self-examination
- Ocular examination
- Sun protection