

Dysplastic Nevi An Update



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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.

Clark WH, et. al. Arch Dermatol. May, 1978

- 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

Clark WH, et. al. Arch Dermatol. May, 1978

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

Clark WH, et. al. Arch Dermatol. May, 1978

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”

Clark WH, et. al. Arch Dermatol. May, 1978



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**

History – Dysplastic nevus syndrome

Dysplastic Nevus Syndrome: A Phenotypic Association of Sporadic Cutaneous Melanoma

Elder DE, et. al. Cancer. Oct, 1980

- 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**

History – Dysplastic nevus syndrome

The Dysplastic Nevus Syndrome: Our definition

Elder DE, et al. Am J Dermatopathol. Oct, 1982

- 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 2nd decade
 - 6th 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

Rhodes AR, et. al. JAMA. Dec, 1987.

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

Halpern AC, et al. J Invest Dermatol. Mar, 1993

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**

Shors AR, et. al. Br J Dermatol. Nov, 2006.

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

- 20,275 nevi examined (1989-1996).
- 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

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

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