Disclosures

Consultant for Myriad Genetics and for SciBase
(might try to sell you a book, as well)

Multidimensional Pathway Classification of Melanocytic Tumors
WHO 4th Edition, 2018

Epidemiologic, Clinical, Histologic and Genomic Aspects of Melanoma

David E. Elder, MB ChB, FRCPA
University of Pennsylvania, Philadelphia, PA, USA
Napa, May, 2018
Malignant Melanoma

• A malignant tumor of melanocytes
• Not all melanomas are the same – variation in:
  – Epidemiology – risk factors, populations
  – Cell/Site of origin
  – Precursors
  – Clinical morphology
  – Microscopic morphology
  – Simulants
  – Genomic abnormalities

Incidence of Melanoma
CSD/Site-Related Classification

- Bastian’s CSD/Site-Related Classification (Taxonomy) of Melanoma
  - “The guiding principles for distinguishing taxa are genetic alterations that arise early during progression; clinical or histologic features of the primary tumor; characteristics of the host, such as age of onset, ethnicity, and skin type; and the role of environmental factors such as UV radiation.”

2018 WHO Classification of Melanoma

- Integrates Epidemiologic, Genomic, Clinical and Histopathologic Features
- Assists in sensitivity, specificity and reproducibility of diagnosis by providing a conceptual morphologic framework
- Provides a context for selection of therapy:
  - Targeted therapy directed against oncogenes
  - Immune therapy directed against neoantigens
Fourth Edition WHO Classification

- 4e WHO Classification, to be published in 2018, defines 9 “Pathways” to melanoma
- “Pathway” concept is based on epidemiologic, clinical, histological, and genomic attributes of the lesions
- Term attributable to Whiteman et al (Brisbane, AU) - distinguished two pathways for common cutaneous melanomas:
  - “Pathways” to melanoma reflects evolution of melanomas from benign precursor lesions through intermediate or dysplastic lesions to radial (low risk) and vertical growth phase melanomas, all in particular epidemiologic and genomic contexts:
    - e.g. Junctional Nevus - Dysplastic Nevus - RGP Melanoma - VGP Melanoma – Low CSD - BRAF/NRAS
    - Blue nevus – Cellular Blue Nevus (CBN) – Melanoma in Blue Nevus (MBN) – No or Variable CSD - GNAQ/GNA11 driver oncogenes

Pathways in Melanoma

- The pathways reflect evolution of melanomas from benign precursor lesions through intermediate or dysplastic lesions to radial (low risk) and vertical growth phase melanomas, all in particular epidemiologic and genomic contexts:
  - e.g. Junctional Nevus - Dysplastic Nevus - RGP Melanoma - VGP Melanoma – Low CSD - BRAF/NRAS
  - Blue nevus – Cellular Blue Nevus (CBN) – Melanoma in Blue Nevus (MBN) – No or Variable CSD - GNAQ/GNA11 driver oncogenes

Tumor Progression in Melanoma

- Precursor Nevus
- Radial Growth Phase (RGP)/MIS
- Vertical Growth Phase (VGP)
- Not obligate
- Steps can be skipped

Most of the histopathologic “classifiers” for melanoma are attributes of the radial growth phase –
- Pagetoid proliferation
- Lentiginous proliferation
The Genetic Evolution of Melanoma from Precursor Lesions. Shain et al., NEJM 2015.

- Precursor lesions initiated by mutations of genes that activate MAP kinase pathway.
- Uniquely benign precursor had BRAF V600E mutations exclusively.
- "Intermediate" lesions were enriched for NRAS and additional driver mutations.
- TERT promoter mutations were present in intermediate lesions and melanomas in situ.
- Biallelic inactivation of CDKN2A exclusively found in invasive melanomas.
- The study identified an intermediate category of melanocytic neoplasia, characterized by the presence of more than one pathogenic genetic alteration and distinctive histopathological features.

New Classification

- The new classification incorporates benign, intermediate or "borderline" and malignant lesions.
- The benign lesions have a single genomic abnormality (e.g. BRAF V600E).
- The intermediate lesions typically have two genomic abnormalities:
  - e.g. hemizygous loss of CDKN2A, TERT promoter mutations, BAP1 loss.
- They have architectural and cytological features different from benign lesions (architectural disorder and cytological atypia):
  - e.g. dysplastic nevi, deep penetrating nevus (DPN), Pigmented Epithelioid Melanocytoma (PEM), BAP1 deficiency “Melanocytomas”

Classification of Melanoma

WHO, 2018

- Pathway I. Low CSD Melanoma/Superficial Spreading Melanoma (SSM)
- Pathway II. High CSD Melanoma/Lentigo Maligna Melanoma (LMM)
- Pathway III. Desmoplastic Melanoma
- Pathway IV. Malignant Spitz Tumor
- Pathway V. Acral Melanoma
- Pathway VI. Mucosal Melanoma
- Pathway VII. Melanoma in Congenital Nevus (MCN)
- Pathway VIII. Melanoma in Blue Nevus (MBN)
- Pathway IX. Uveal Melanoma
- Variable Pathways: Nodular Melanoma
Table 1. Classification of Melanocytic Tumors by Epidemiologic, Clinical, Histopathologic and Genomic Attributes

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Low UV</th>
<th>High UV</th>
<th>Low to No (or Variable) CSD</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

**Low UV**

Pathway I: Low CSD Melanoma
Superficial Spreading Melanoma

Based on acquired nevus (junctional, compound, dermal)

- Low-grade Dysplasia
- High-grade Dysplasia
- Superficial Spreading Melanoma
- Lentiginous junctional nevus
- Compound dysplastic nevus
- Superficial spreading or "pagetoid" melanoma

High UV
Pathway II
High CSD Melanoma (LM)

Pathway III
Desmoplastic Melanoma

Pathway IV
No UV
Malignant Spitz Tumor
Spitz Nevus
Atypical Spitz Nevus
STUMP
Malignant Spitz Tumor
vs. Malignant Spitzoid Tumor, vs. "Melanoma with Spitzoid Features"

WHO classification of skin tumours/

Pathway V

Acral Melanoma

Atypical melanocytic proliferation
Melanoma in situ

Acral lentiginous melanoma

KIT, NRAS, BRAF, HRAS, HRAS2, NF1, NF1, NTRK3, ALK, NF1, CDKN2A, TERT, CCND1, GAB2

2018 Proposed Classification of Melanoma, Precursors and Simulants
Your Diagnosis

Nevus?
Melanoma?

5 years later ...
Local recurrences are relatively common in acral melanomas

Compared to SSM e.g. of the trunk
Field Effect in ALM

- Genomically abnormal melanocytes extending as much as 1 cm from detectable border
- May partly explain propensity of these lesions for local recurrences
- (Bastian et al. Cancer Research, 2000)

### Pathways V No UV

<table>
<thead>
<tr>
<th>Acral Melanoma</th>
<th>Acral Melanoma in situ</th>
<th>Acral lentigious melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical melanocytic proliferation</td>
<td>Melanoma in situ</td>
<td>KIT, NRAS, BRAF, HRAS, KRAS, NTRK3, ALK, NF1</td>
</tr>
<tr>
<td>CDK5RA, TERT, CCND1, GAB2</td>
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</tbody>
</table>

Acral Melanomas and Simulants

- Epidemiology: Role of Trauma (not UV).
- Phenotype: Absolute incidence is about the same in all skin types (relatively higher in low incidence populations)
- Genomic: High copy number variation, and mutation/amplification of Cyclin D and KIT, among other oncogenes.
- Acral nevi are the major simulants

### Genetic Alterations in Primary Acral Melanoma and Acral Melanocytic Nevus in Korea

Moon KR, Cho YJ, Kim JH, Je J, Shin MK, Shin HJ, Lee JB, Yoo HS. Department of Dermatology, Chonnam National University Medical School, Gwangju, South Korea.

**Common Mutated Genes Show Distinct Cytomorphological Features.**

- 85 Korean patients with acral melanocytic neoplasms.
- Performed next-generation sequencing and evaluated the genetic and clinical correlations.
- The five most common mutations were BRAF (34.4%), NRAS (21.9%), NF1 (17.2%), GNAQ (17.2%), and KIT (10.9%).
- In the 21 acral melanocytic nevi, those five gene mutations were also common.
- Copy number variations were also frequently detected in 75% of acral melanomas and 47.6% of acral melanocytic nevi, and amplification was more common than deletion in both lesions.
  - BRAF mutation was associated with round epithelioid cells and NRAS and NF1 mutations with bizarre cells.
  - NF1 and GNAQ mutations showed elongated and spindle cells with prominent dendrites in acral melanomas.
  - KIT mutations were common in amelanotic acral melanoma.
- This study suggests that common mutated genes are associated with distinct cytological features in acral melanocytic lesions.

Acral Nevus vs Acral Melanoma

- Overlapping histopathologic features of acral nevus, special site nevus, dysplastic nevus, and melanoma

- Size: important criteria for distinction
  - Excisional biopsy is recommended rather than punch biopsy

- Uncertainty is common – can use descriptive terminology
  - Intraepidermal Atypical Melanocytic Proliferation of Uncertain Significance (IAMPUS), SAMPUS, or MELTUMP
  - Differential diagnosis (e.g. favor acral junctional nevus, cannot rule ALM in situ) should be expressed.

Next Case

Lesion of thumb in a 65 year old man
Your diagnosis

Nevus?
Melanoma?
Amputation specimen for “biopsy-proven” melanoma

Extensive RGP and Bulky VGP
Our Diagnosis

Malignant melanoma, acral-lentiginous, Breslow thickness 3.2 mm
Subtle proliferation at periphery probably melanoma, not nevus, could result in recurrence if left on margin

Next Case
Your diagnosis
Nevus?
Melanoma?

Your diagnosis
Margin negative?
Margin Positive?

Next Case
Your diagnosis

Nevus?
Melanoma?
Our Diagnosis

Malignant melanoma, acral-lentiginous type, present at a peripheral margin (same as Previous Case)

Acral-Lentiginous Melanoma (ALM)

- Lentiginous radial growth phase
- Continuous basal proliferation of uniformly atypical melanocytes
- Lacks solar elastosis ("no CSD")
- Often a spindle cell vertical growth phase
- Vertical growth phase often desmoplastic and/or neurotropic (local recurrence risk)

Acral Nevus and RGP Melanoma

Sook Jung Yun, MD, PhD
Associate Professor, Department of Dermatology
Chonnam National University Medical School
Gwangju, South Korea

Histopathology of Acral Nevus

- Junctional or compound nevi
  - only slight to moderate atypia
- Large, vertically oriented junctional nests
  - Discrete melanin columns in cornified layer
- Lentiginous melanocytic proliferation confined to epidermal rete
- Limited degree of pagetoid scatter (up to 86.5%)
  - “Melanocytic acral nevus with intraepidermal ascent of cells (MANIAC)” — Le Boit, UCSF
- Transepidermal elimination
- Ridge and furrow patterns may be helpful
  - Clinical/dermoscopic correlation important

Dermoscopy for Acral Nevus vs Melanoma

SJ Yun S Korea
Histopathology of Acral Nevus


Acral Nevus; Parallel Furrow Pattern

Acral Melanoma; Parallel Ridge Pattern

Tissue section: Dermatoglyphics Vertical

Furrow pigment column
Acral Junctional Nevus Versus Acral Lentiginous Melanoma In Situ
A Differential Diagnosis That Should Be Based on Clinicopathologic Correlation

<table>
<thead>
<tr>
<th>Tissue section: Dermatoglyphics Parallel</th>
<th>SJ Yun S Korea</th>
</tr>
</thead>
</table>

Acral Junctional Nevus Versus Acral Lentiginous Melanoma In Situ
A Differential Diagnosis That Should Be Based on Clinicopathologic Correlation

<table>
<thead>
<tr>
<th>Acral junctional nevus</th>
<th>Acral lentiginous melanoma</th>
</tr>
</thead>
</table>

Histopathological Differential Diagnosis is not easy!

Size Matters!

Acral Nevus vs Acral Melanoma

- Overlapping histopathologic features of acral nevus, special site nevus, dysplastic nevus, and melanoma
- **Size**: important criteria for distinction
  - Excisional biopsy is strongly recommended over punch biopsy
  - Punch biopsy could be diagnostic of melanoma — “never” of nevus!
- Intraepidermal Atypical Melanocytic Proliferation of Uncertain Significance (IAMPUS), MELTUMP
  - Descriptive term, D/Dx should be expressed.
Clinicopathologic Analysis of 335 Acral Nevi
Yun SJ, Chonnam University S Korea

<table>
<thead>
<tr>
<th>Histopathologic Features</th>
<th>Lentigo (9%)</th>
<th>Junctional Nevus (3%)</th>
<th>Compound Nevus (3%)</th>
<th>Intradermal Nevus (1%)</th>
<th>Congenital Compound Nevus (5%)</th>
<th>Congenital Intradermal Nevus (3%)</th>
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<tbody>
<tr>
<td>Nest</td>
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<td>3 (nests dominant)</td>
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<td>1 (1 nests)</td>
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<td>24.3%</td>
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<tr>
<td>2 (2-5 nests)</td>
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<td>0%</td>
<td>7.4%</td>
<td>0.1%</td>
<td>0%</td>
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<tr>
<td>3 (&gt;5 nests)</td>
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<td>2.5%</td>
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<td>0%</td>
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<td>0%</td>
<td>23.3%</td>
<td>14.3%</td>
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<tr>
<td>2 (2-5 nests)</td>
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<td>0%</td>
<td>22.1%</td>
<td>14.3%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>3 (&gt;5 nests)</td>
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<td>0%</td>
<td>3.2%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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</tbody>
</table>

Confluence: Junctional nevus (21.6%), Compound nevus (25.3%)
Discohesion: Junctional nevus (39.5%), Compound nevus (35.4%)

SJ Yun S Korea

5/22/2018
### Clinicopathologic Analysis of 335 Acral Nevi

<table>
<thead>
<tr>
<th>Histopathologic Features</th>
<th>Lentigo (48%)</th>
<th>Junctional Nevus (164%)</th>
<th>Junctional Nevus (8%)</th>
<th>Junctional Nevus (2%)</th>
<th>Compound Nevus (99%)</th>
<th>Congenital Compound Nevus (9%)</th>
<th>Congenital Intradermal Nevus (3%)</th>
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<tr>
<td>Single cell Proliferation</td>
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<td>0%</td>
<td>0%</td>
<td>0%</td>
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<td>Focal continuous</td>
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<td>Noncontinuous</td>
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<td>44%</td>
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<td>Prominent</td>
<td>3</td>
<td>4.8%</td>
<td>3.4%</td>
<td>3.4%</td>
<td>7.1%</td>
<td>9%</td>
<td>1%</td>
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</table>

**Continuous or focal continuous proliferation of single cells:**
- Junctional nevus (42.4%), Compound nevus (54.5%)

**Prominent dendrites:**
- Junctional nevus (5.6%), Compound nevus (7.1%)
Single cell proliferation

Parallel Furrow pattern (melanin column)

Pagetoid scatter

Melan A

Atypical melanocytes with prominent dendrites

Your Diagnosis? Nevus? Melanoma?

Excise Completely!
Single cells proliferation

Atypical melanocytes with prominent dendrites

Junctional nevus with atypia (or IAMPUS)

Your Diagnosis? Nevus? Melanoma?
Clinicopathologic Analysis of 335 Acral Nevi

<table>
<thead>
<tr>
<th>Histopathologic features</th>
<th>Lentigo (63)</th>
<th>Junctional Nevus (162)</th>
<th>Compound Nevus (99)</th>
<th>Intradermal Nevus (9)</th>
<th>Congenital compound Nevus (5)</th>
<th>Congenital Intradermal Nevus (3)</th>
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<tbody>
<tr>
<td>Pagetoid scatter</td>
<td>1 (mod.)</td>
<td>17.3%</td>
<td>53.1%</td>
<td>4.5%</td>
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<td>Grade</td>
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<tr>
<td>Cell</td>
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<td>17.3%</td>
<td>53.1%</td>
<td>4.5%</td>
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<td>0%</td>
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<tr>
<td>Level</td>
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<td>3.2%</td>
<td>3.1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Pagetoid scatter: Junctional nevus (56.2%), Compound nevus (57.5%)
Pagetoid cells in entire epidermis: Junctional nevus (19.8%), Compound nevus (15.5%)

Diagnosis of Acral Nevus vs. Subtle Acral Melanoma In Situ

“The only good acral nevus is a completely excised acral nevus”.

Table 1. Classification of Melanocytic Tumors by Epidemiologic, Clinical, Histopathologic and Genomic Attributes
**Pathway VI**
No UV
Mucosal Melanoma
Atypical melanosis
IAMPUS/ SAMPUS
Mucosal lentigious melanoma
KIT, NRAS, KRAS, or BRAF,
NF1, CDKN2A, SF3B1, CCND1, CDK4, MDM2

Role of UV:
Low UV
High UV
Low to No (or Variable) CSD
Pathway:
I
II
III
IV
V
VI
VII
VIII
IX

Low-CSD Melanoma
Superficial Spreading Melanoma
High-CSD Melanoma (LMM)
Desmoplastic Melanoma
Spitz Melanoma
Acral Melanoma
Mucosal Melanoma
Melanoma in Congenital Nevus
Melanoma in Blue Nevus
Uveal Melanoma

Benign Nevus
IAMP
IAMP
Spitz Nevus
IAMP
Melanosis Congenital Nevus (CN)
Blue Nevus
?

Borderline Low
Low Grade Dysplasia
Bap-1 Deficiency
Melanocytoma/MELTUMP
DPN Melanocytoma/MELTUMP
PEM Melanocytoma/MELTUMP
? IAMP
? IAMP
Atypical Spitz nevus
Atypical melanocytic proliferation
Atypical melanosis
Nodular proliferation in CN
Cellular Blue Nevus
Uveal nevus

Borderline High
High Grade Dysplasia
Lentigo maligna
Melanoma in situ
STUMP Melanoma in situ
IAMPUS/SAMPUS MIS in CN
Atypical CBN
?

Malignant
Superficial Spreading Melanoma
Melanoma in BPDM (rare)
Melanoma in DPN (rare)
Melanoma in PEM (rare)
Lentigo Maligna Melanoma
Desmoplastic Melanoma
Malignant Spitz Tumor
Acral lentiginous melanoma
Mucosal lentiginous melanoma
Melanoma in CN
Melanoma ex Blue Nevus
Uveal melanoma

Common mutations
BRAF V600E, NRAS
(BRAF or NRAS)+BAP1 (BRAF, MEK1, or NRAS)+(CBNN1 or APC)
(BRAF+PRKAR1A) or PRKCA
NRAS, BRAF non-V600E, KIT, NF1
NF1, ERBB2, MAP2K1, MAP3K1, BRAF, EGFR, MET, HRAS, ALK, ROS1, RET, NTRK1, NTRK3, BRAF, MET, KIT, NRAS, BRAF, HRAS, KRAS, NTRK3, ALK, NF1
KIT, NRAS, KRAS, or BRAF, NRAS, BRAF
V600E (small lesions), BRAF

TERT, CDKN2A, TP53, PTEN,
TERT, CDKN2A, TP53, PTEN,
RAC1
TERT, NFKBIE, NRAS
PIK3CA PTPN11
CDKN2A
CDKN2A, TERT
CCND1, GAB2
NF1, CDKN2A
SF3B1, CCND1, CDK4, MDM2
BAP1, EIF1AX
SF3B1, EIF1AX, BAP1

Table 1. Classification of Melanocytic Tumors by Epidemiologic, Clinical, Histopathologic and Genomic Attributes
Pathway VII
No/Variable UV
Melanoma in Congenital Nevus (MCN)
Congenital Nevus (CN)
Nodular proliferation in CN
? MIS in CN
Melanoma in CN
NRAS, BRAF V600E (small lesions), BRAF
WHO classification of skin tumors /

Table 1. Classification of Melanocytic Tumors by Epidemiologic, Clinical, Histopathologic and Genomic Attributes

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Low UV</th>
<th>High UV</th>
<th>Low to No (or Variable) UV</th>
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<tbody>
<tr>
<td>I</td>
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<td>V</td>
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<td>VIII</td>
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<tr>
<td>IX</td>
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</tbody>
</table>

Genes
- BRAF V600E, NRAS
- (BRAF or NRAS)+BAP1
- (BRAF, MEK1, or NRAS)+(CBNN1 or APC)
- (BRAF+PRKAR1A) or PRKCA
- NRAS, BRAF V600E (small lesions), BRAF
- GNAQ, GNA11, CYSLTR2, or PLCB4
- TERT, CDKN2A, TP53, PTEN
- TERT, NFKBIE, NRAS
- PIK3CA PTPN11
- CDKN2A, TERT
- CCND1, GAB2
- NF1, CDKN2A
- SF3B1, CCND1, MDM2
- BAP1, EIF1AX
- SF3B1, EIF1AX, BAP1
Pathway VIII

NOD/Variable UV
Melanoma in Blue Nevus (MBN)

Blue Nevus

Cellular Blue Nevus

Atypical CBN

Melanoma in Blue Nevus

GNAQ, GNA11, CYSLTR2, BAP1, EIF1AX SF3B1

• Background blue nevus
• Cellular blue nevus
• Melanoma in Blue Nevus (MBN)

Nodular Melanoma

Clinical Features

• Detectable RGP is absent by definition
  – Tumorigenic melanoma without an adjacent nontumorigenic component
  – Short-lived RGP may be obliterated by the developing tumor.
  – Nodular variants probably exist in all pathways

• ABCD criteria may not apply
  – Lesions are often symmetrical nodules/papules with raised discrete borders, fairly uniform color, diameter not always > 6 mm

• Prognosis is similar to other melanomas of same microstage
Table 1. Classification of Melanocytic Tumors by Epidemiologic, Clinical, Histopathologic, and Genomic Attributes

<table>
<thead>
<tr>
<th>Classification</th>
<th>Epidemiologic</th>
<th>Clinical</th>
<th>Histopathologic</th>
<th>Genomic Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular melanoma</td>
<td>Low UV</td>
<td>Low to No (or Variable) UV</td>
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<tr>
<td>Superficial Spreading Melanoma</td>
<td>Low CSD</td>
<td>High CSD</td>
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<tr>
<td>Desmoplastic Melanoma</td>
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<td>Spitz Melanoma</td>
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<td>Acral Melanoma</td>
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<tr>
<td>Mucosal Melanoma</td>
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<tr>
<td>Melanoma in Congenital Nevus</td>
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<tr>
<td>Melanoma in Blue Nevus</td>
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<tr>
<td>Uveal Melanoma</td>
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<tr>
<td>Benign Nevus</td>
<td>High UV</td>
<td>Low UV</td>
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<tr>
<td>Melanosis Congenital Nevus (CN)</td>
<td>Low CSD</td>
<td>High CSD</td>
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<tr>
<td>Melanoma in Blue Nevus</td>
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<tr>
<td>Cellular Blue Nevus</td>
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<tr>
<td>Uveal nevus</td>
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<tr>
<td>Borderline Low Grade Dysplasia</td>
<td>Low CSD</td>
<td>High CSD</td>
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<td>Melanocytoma</td>
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<td>Melanocytoma</td>
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<tr>
<td>Atypical Spitz nevus</td>
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<tr>
<td>Atypical melanocytic proliferation</td>
<td>High CSD</td>
<td>Low CSD</td>
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<td>Atypical melanosis</td>
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<tr>
<td>Nodular proliferation in CN</td>
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<td>Cellular Blue Nevus</td>
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<td>Borderline High Grade Dysplasia</td>
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<td>Lentigo maligna Melanoma</td>
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<td>Melanoma in situ</td>
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<td>STUMP Melanoma</td>
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<td>Uveal melanoma</td>
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<tr>
<td>Superficial Spreading Melanoma</td>
<td>Low CSD</td>
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<tr>
<td>Melanoma in BPDM (rare)</td>
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<td>Melanoma in DPN (rare)</td>
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<td>Melanoma in PEM (rare)</td>
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<tr>
<td>Desmoplastic Melanoma</td>
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<td>Malignant Spitz Tumor</td>
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<tr>
<td>Acral lentiginous melanoma</td>
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<tr>
<td>Uveal melanoma</td>
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</table>

Common mutations:
- BRAF V600E, NRAS
- (BRAF or NRAS)+BAP1
- (BRAF, MEK1, or NRAS)+APK1 or APC
- (BRAF+PRKAR1A) or PRKCA
- NRAS, BRAF non-V600E, KIT, NF1
- NF1, ERBB2, MAP2K1, MAP3K1, BRAF, EGFR, HRAS, ALK, ROS1, RET, NTRK1, NTRK3, BRAF, MET, KIT, NRAS, BRAF, HRAS, KRAS, NTRK3, ALK, NF1
- KIT, NRAS, KRAS, or BRAF, NRAS, BRAF V600E (small lesions), BRAF
- GNAQ, GNA11, CYSLTR2, or PLCB4

TERT, CDKN2A, TP53, PTEN, TERT, CDKN2A, TP53, PTEN, RAC1
- TERT, NFKBIE, NRAS, PIK3CA, PTPN11
- CDKN2A, TERT
- CDKN2A, TERT, CCND1, GAB2
- NF1, CDKN2A
- SF3B1, CCND1, CDK4, MDM2
- BAP1, EIF1AX
- SF3B1, EIF1AX, BAP1
New Classification of Melanoma

- Integrates Epidemiology, Genomic, Clinical and Histopathologic Features
- Assists in reproducibility of diagnosis by providing a conceptual morphologic framework
- Provides a context for selection of therapy:
  - Targeted therapy directed against oncogenes
    - Driver oncogene
  - Immune therapy directed against neoantigens
    - Mutation burden – high in high CSD, low in mucosal

Acknowledgements

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Thank You!