What's New in Dermatopathology
Melanocytic proliferations

Aleodor (Doru) Andea, MD, MBA
Associate Professor of Pathology and Dermatology
Director of Dermatopathology Molecular Diagnostic Laboratory
University of Michigan
Ann Arbor, MI
andeaa@med.umich.edu
@DoruAndea

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Dr. Aleodor Andea declares he has no conflict(s) of interest to disclose.

Overview

1. Case based presentation
2. Updates in molecular ancillary studies for the diagnosis of difficult melanocytic tumors (SNP microarrays)
3. Updates in diagnosis and prognosis of few melanocytic entities

• Why do we need more stuff?

Common nevus
Melanoma

PLEASE TURN OFF YOUR CELL PHONES
• A small proportion have ambiguous histology

• 40-year old woman with a papule on the right shoulder
• Clinical R/O BCC

• Melanocytic neoplasm with borderline features between nevus and melanoma
• Suspicious for nevoid melanoma
What else we can do?

Molecular studies

- Genomic instability in melanoma
- Detection of numerical abnormalities in the tumor genome (CGH/SNP and FISH)
- Mass spectrometry
- Gene expression profile
- Identification of mutations (TERT gene promoter)

Comparative Genomic Hybridization (CGH)/Single Nucleotide Polymorphism (SNP) arrays

- Screens the entire genome for gains and losses in DNA material in one experiment
- Variants:
  - Array based CGH—Gains and Losses
  - Array based SNP—Gains, Losses and Loss of Heterozygosity
SNP arrays

- Copy number changes
- Allele peak

SNP arrays

- Copy number changes
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SNP arrays

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SNP arrays

- Copy number changes
- Allele peak
- Mutation data
  - BRAF
  - NRAS
  - PTEN
  - TP53
Univ of Michigan Cohort

Melanoma

• No gains or losses
• BRAF V600E

Univ of Michigan Cohort

Melanoma

• 19 CNA
• 13 losses
• 6 gains
• BRAF V600E

Univ of Michigan Cohort

Melanoma

• 19 CNA
• 13 losses
• 6 gains
• BRAF V600E

Compound nevus

• No gains or losses
• BRAF V600E

Primary melanoma
Metastatic melanoma

- 30 CNA
  - 25 gains
  - 5 losses
- 3 CN-LOH
- BRAF V600K
- Chr 22 CN-LOH
- Chr 9p21 homozygous loss (CDKN2A)
- Chr 1p gain (NRAS)
- NRAS Q61R
- Chr 13q loss (BRCA2)
- Chr 22 CN-LOH
- Chr 1p gain (NRAS)
- Chr 13q loss (BRCA2)
- NRAS Q61R
Nevoid melanoma

This seems easy enough...

- No abnormalities – GOOD
- Abnormalities – BAD

- Not that simple

Not all abnormalities are bad

- Some can be used to classify nevi

BAP-1 negative nevus (BAP-oma)

3p loss (BAP-1 locus)

BRAF V600E
BAP1 IHC

10 days old AA newborn

Giant congenital nevus with several nodules

CGH
OncoScan™
Affymetrix

• Result: Losses of whole chromosomes 3, 4, 5, 10, 11, 13, 14, 16, 17, 18, 21

1 year old

Proliferative nodule in a congenital nevus

More problems

• How many abnormalities do we require for a melanoma diagnosis
Histological classification | # of cases with at least one significant copy number variation | Average # CNV
--- | --- | ---
Nevi | 0/6 (0%) | 0
Atypical nevi | 3/15 (20%) | 1.6 (1-2)
Ambiguous | 15/25 (60%) | 6.3 (1-25)
Melanoma | 35/39 (90%) | 21.7 (1-69)

Sensitivity: 90%
Specificity: 87%

• >=3 abnormalities significant (but with exceptions)
  • Whole chromosomal abnormalities in proliferative nodules
  • Isolated homozygous deletion of 9p21 favors melanoma
  • Others to come....

Ultimate question
• Can CNV number and/or pattern predict adverse outcome in borderline lesions?
  • Unfortunately not too many studies

Ambiguous cases with clinical follow up

Practical algorithm for use of molecular studies
Melanocytic lesion

Histologic examination

Definitive diagnosis

No further testing

Ambiguous lesion

Histologic examination

Definitive diagnosis

No further testing

Molecular testing

Ambiguous lesion

Histologic examination

Favor benign

Borderline

Favor malignant

Mol -

Mol +

Mol -

Mol +

Ambiguous lesion

Histologic examination

Borderline

Favor benign

Favor malignant

Mol +

Mol -

Mol +

Mol -

Borderline favor

nevus

Borderline favor

melanoma

Malignant

Nevus

Borderline
**Histologic examination**

**Ambiguous lesion**

- Favor benign
- Favor malignant

- Mol -
- Mol +

- Borderline

**Risk assessment**

- Definitive diagnosis
- No further testing

- Melanocytic lesion
- Nevus

**Cost and TAT**

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
<th>TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP/CGH array</td>
<td>$1,500-$2,400</td>
<td>14-21 days</td>
</tr>
<tr>
<td>FISH</td>
<td>$800-$1,200</td>
<td>3-7 days</td>
</tr>
</tbody>
</table>

**Microarray vs. FISH**

- Order Microarray if
- Order FISH if
Microarray vs. FISH

• Order Microarray if
  • Can afford
  • Have enough material
    • > 1mm²
    • >30% tumor purity
    • 10 unst @ 10 microns
  • Can wait 2-3 weeks

Advantage: higher sensitivity

• Order FISH if
  • Microarray not covered
  • Not enough material
  • Only few slides
  • Superficial lesions
  • Tumor infiltrated by benign cells/inflammation

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Disadvantage: lower sensitivity, higher false positive (lower specificity)

Key points

• CNVs can assist in the diagnosis of melanocytic lesions
• Should be used only in ambiguous lesion
• Molecular data should not overturn histologic impression
• >=3 abnormalities – significant for melanoma
• Understand the molecular report

30 y/o male blue-colored plaque on the scalp with subcutaneous nodules

Bx from the plaque
Large plaque-type blue nevus with subcutaneous cellular nodules

6 years later
Melanoma ex cellular blue nevus

- Aka Malignant blue nevus
Melanomas Associated With Blue Nevi or Mimicking Cellular Blue Nevus
Clinical, Pathologic, and Molecular Study of 11 Cases Displaying a High Frequency of GNA11 Mutations, BAP1 Expression Loss, and a Predilection for the Scalp.


- Predilection for scalp
- Scalp lesions with GNA11 mutations (as opposed to GNAQ in other sites)
- Loss of BAP1 associated with scalp location and poor prognosis
Genomic copy number analysis of a spectrum of blue nevi identifies recurrent aberrations of entire chromosomal arms in melanoma ex blue nevi

May P Chiu1,2, Alcudia A Andujar1,2, Paula W Hammar1,2, Allison R Darbyson1, Rajiv M Patel3,2, Mia Wang1, Patricia Rubenhaus1, Gary J Fasching1, Timothy M Johnson1 and Douglas R Fidler3

1Department of Pathology, University of Michigan, Ann Arbor, MI, USA and 2Department of Dermatology, University of Michigan, Ann Arbor, MI, USA

Blue nevus: 5
Atypical blue nevi: 10
Melanoma ex blue nevus: 9

Atypical blue nevi may show few aberrations.

3p loss may have prognostic implications in MBN.
Key points

- MBN usually arise in a preexisting blue nevus
- BAP-1 loss: marker for adverse outcome

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**QUESTIONS?**
• 79 y/o man
• Pigmented lesion on left medial finger for 6 years
• Slowly growing
Current case

Acral lentigious MIS

Lentigo

- Recurrence after 4 years
Acral lentiginous melanoma

- 13 patients
- Bland proliferation of melanocytes
- Not sufficient for MIS

What else we could have done?

Fluorescence in situ hybridization
FISH for melanocytic tumors

• Evaluate for copy number alterations

• Original panel:
  • 6p25 (RREB1) — gains
  • 6q23 (MYB) — losses
  • 11q13 (CCND1) — gains

• Expanded panel:
  • 8q24 (MYC) — gains
  • 9p21 (CDKN2A) — homozygous loss

Fluorescence in situ hybridization

Key points

• When faced with acral pigmented lesions with histologically subtle atypical ALWAYS ask for the clinical impression

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