Melanoma CPC: Demystifying the Molecular Maze, A Diagnostic & Prognostic Update

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No Relevant Disclosures
Case #1

A Baffling Baldhead Blain
What Is Your Diagnosis?
Desmoplastic Melanoma
Precis

- AKA: Neurotropic, 1st described in 1971
- Rare ~ 4% of melanomas, 2♂ : 1♀; 66 years, Caucasian
- 50% H&N, 30% EXT, 17% trunk, 1/3 no surface abnormality
- 50% in accordance w/ lentigo-magna
- 27% correct DX on 1st biopsy, avg. depth 5.5mm, 1/3 no epidermal component
- Bland Spindled cells w/ desmoplastic, neurotropism & lymphoid aggregates
- Antigen infidelity, F (+) SMA, F (-) mart-1, melanoma, tyrosinase, MITF, HMB-45
- 40% pure, 60% mixed w/ conventional melanoma
- Overall survival 72%♀, EXT, ↓ age, no neurotropism, pure compositions, better prognosis
- Nodal involvement rare, SLNB?, WLE 2cm > 1cm prognosis, XRT
**Precis**

- **AKA:** Neurotropic, 1\(^{st}\) described in 1971
- **Rare ~ 4% of melanomas,** 2\(^{♂}\) : 1\(^{♀}\); 66 years, Caucasian
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Molecular Developments

- ↑ Clusterin expression, loss of melangogenesis genes e.g. tyrosinase
- Multiple genetic (non-driver) alterations, UV signature, NF-1, P53, PD-1
Case #2

BLINDED BY THE LIGHT!
38 year old female s/p excision for invasive melanoma with photosensitivity
Figure 2: Development Study

Class 1: 5yr MFS=100%

Class 2: 5yr MFS=38%

ROC=0.9268
Accuracy=89%
Sensitivity=100%

Kaplan-Meier plot of distant metastasis-free survival in node-negative Stage I and II melanomas. (n=107; p<0.0001). Dhillon et al, 2012.
Gene Expression Profile Assays

- Multiple genetic loci tested associated with your prognosis
- Stratify patient risk for prognosis and benefit from more aggressive therapy
- Performed on achieved tissue blocks
- Independent prognosticator from traditional demographic or pathologic information
- Decision DX
INDICATIONS FOR MELANOMA GENE EXPRESSION PROFILING

- Histologic features of regression
- Transected invasive melanoma < 0.80mm
- Depth of invasion between 0.50 and 0.80mm
Melanoma Associated Retinopathy

- AKA Cancer associated or paraneoplastic retinopathy
- Cross-reacting melanoma associated antibodies elicited antibodies to retinal proteins
- Rare 1:1,000,000 men = women, mean age 61.8 years, strong association with autoimmunity
- Most common with small cell lung cancer > gynecologic > melanoma
- May antedate or follow established diagnosis
- Usually associated with clinical or microscopic features of regression
- Diagnostic criteria: ERG, anti-retinal antibodies, funduscopic optic disk pallor, retinal pigment mottling, attenuated vasculature
- Treatment delays progression (corticosteroids, IVIG, rituximab)
VEMURAFENIB

- Genetic mutation analysis for targeted therapy
- B-raf analysis (1q34)
- B-raf gene encodes for specific genetic threonine protein kinases
- Regulate MAP/ERK signaling pathway
- MAP/ERK regulates cell division/differentiation
- Mutations associated within lymphoma, colorectal, thyroid, non-small cell lung, and melanoma
- >60% melanomas harbor B-raf mutation
- >90% substitution of glutamic acid for valine at 600# position (V600E)
RAS–RAF Pathway

**Growth factors**

**Normal RAS–RAF pathway signaling**

**Oncogenic BRAF signaling**

RTK → RAS–GTP → Activated RAS → BRAF → MEK → ERK

**Normal activation of RAS by extracellular factors**

Normal cell proliferation and survival

**Mutated BRAF**

Constitutive activation is independent of extracellular factors

Not responsive to normal regulatory signals

Excessive cell proliferation and survival
VEMURAFENIB

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B RAF TESTING

- Versus DNA sequencing (Sangar versus pyroseq testing)
- PCR more sensitive, faster, cheaper than sequencing
- Sequencing more specific, potentially better at detecting V600K, V600D
FUTURE OF MELANOMA & THE LABORATORY/PATHOLOGISTS
<table>
<thead>
<tr>
<th>Cutaneous symptoms</th>
<th>N</th>
<th>Prevalence (%)</th>
<th>Start day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verrucous papilloma</td>
<td>33</td>
<td>79</td>
<td>35 (7–100)</td>
</tr>
<tr>
<td>Hand–foot skin reaction</td>
<td>25</td>
<td>60</td>
<td>61 (8–300)</td>
</tr>
<tr>
<td>Hyperkeratotic follicular rash</td>
<td>23</td>
<td>55</td>
<td>32 (7–80)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>22</td>
<td>52</td>
<td>47 (2–166)</td>
</tr>
<tr>
<td>Hair growth modification</td>
<td>19</td>
<td>45</td>
<td>61 (20–150)</td>
</tr>
<tr>
<td>Xerosis</td>
<td>14</td>
<td>33</td>
<td>57 (2–180)</td>
</tr>
<tr>
<td>Cystic lesion</td>
<td>14</td>
<td>33</td>
<td>108 (7–253)</td>
</tr>
<tr>
<td>Milia</td>
<td>13</td>
<td>31</td>
<td>48 (21–83)</td>
</tr>
<tr>
<td>SCC</td>
<td>11</td>
<td>26</td>
<td>111 (50–515)</td>
</tr>
<tr>
<td>Facial erythema</td>
<td>7</td>
<td>17</td>
<td>62 (10–140)</td>
</tr>
<tr>
<td>Cheilitis</td>
<td>6</td>
<td>14</td>
<td>32 (7–41)</td>
</tr>
<tr>
<td>Panniculitis</td>
<td>6</td>
<td>14</td>
<td>78 (9–240)</td>
</tr>
<tr>
<td>Keratoacanthoma (KA)</td>
<td>6</td>
<td>14</td>
<td>77 (27–172)</td>
</tr>
<tr>
<td>Nipple hyperkeratosis</td>
<td>5</td>
<td>12</td>
<td>76 (30–120)</td>
</tr>
<tr>
<td>Naevi efflorescence</td>
<td>4</td>
<td>10</td>
<td>81 (52–130)</td>
</tr>
<tr>
<td>Severe radiodermatitis</td>
<td>2</td>
<td>5</td>
<td>34 (13–55)</td>
</tr>
</tbody>
</table>
Case #3

ACRAL LESION IN AN ALL-AMERICAN
WHAT IS YOUR DIAGNOSIS?
ACRAL LENTIGINOUS MELANOMA
Melanoma of glabrous/acral non-hair bearing skin

#1 skin cancer among African Americans, Asian Americans; 1.8/1M

3% of melanoma, 36% of melanoma in African Americans; ♂=♀; older age group

↑ risk in African Americans, Asians and Hispanics

Plantar (75%) > Palmar 20% > nail matrix 4% > oral 1% > anal 0.5%

Flat lentiginous like growth (radial) → vertical; 10% amelanotic

Distinctive dermatoscopic findings

Pathology tricky, dendritic melanocytes, confluence, acrosyringeal extension; 36% misdiagnosis

Prognosis worse, 94% 5-7 versus 77%, 71% versus 40% stage T1A at diagnosis

C-kit amplification, c-kit mutations ~ 50% of lesions (triple negative)

C-kit (mast/stem cell growth factor receptor, receptor tyrosine kinase proto-oncogene; imatinib (Gleevac)
Precis

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Case # 4

SPOOKY SPITZ AND THE SWORD OF DAMOCLES
**Gene Expression May Precede Visible Morphologic Change.**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UV Damage Event</td>
</tr>
<tr>
<td>2</td>
<td>Hotspot Driver Mutations</td>
</tr>
<tr>
<td>3</td>
<td>PRAME &amp; LINC Gene Expression*</td>
</tr>
<tr>
<td>4</td>
<td>Microscopic Changes</td>
</tr>
<tr>
<td>5</td>
<td>Macroscopic Changes</td>
</tr>
</tbody>
</table>

**ULTRAVIOLET RADIATION**

<table>
<thead>
<tr>
<th>Mutation Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF V600E</td>
</tr>
<tr>
<td>TERT + NRAS + TERT</td>
</tr>
<tr>
<td>BRAF V600K + TERT</td>
</tr>
<tr>
<td>BRAF + NRAS + TERT</td>
</tr>
<tr>
<td>LINC + PRAME + ...</td>
</tr>
</tbody>
</table>

**Integrated Diagnosis (1-5)**

- Benign Lesion
- Atypical Lesion
- Melanoma In Situ
- Invasive Melanoma

The PLA focuses on the optimized expression targets of PRAME and LINC.
The PLA Samples Gene Expression Across the Entire Lesion

- Cellular Extension of Melanocyte
- Melanin Granules
- Golgi Apparatus
- Melanocyte Nucleus
- Basal Lamina
Highly Validated with Proven Clinical Utility

The DermTech PLA is an objective test intended for use on pigmented lesions suspicious for melanoma that meet 1 or more ABCDE criteria to provide accurate, actionable information.\(^9\)

The PLA collects RNA to measure gene expression across the entire lesion. Gene expression technology improves the negative predictive value (NPV) for early melanoma detection.

- 91% sensitivity
- Clinicians follow the guidance of the test in over 98% of cases
- >99% NPV
Development and validation of a noninvasive 2-gene molecular assay for cutaneous melanoma

Pedram Gerami, MD, Zuxu Yao, PhD, David Polsky, MD, PhD, Burkhard Jansen, MD, Klaus Busam, MD, Jonhan Ho, MD, Mary Martin, MD, and Laura K. Ferris, MD, PhD

The publisher's final edited version of this article is available at J Am Acad Dermatol
See other articles in PMC that cite the published article.

Abstract

Background
Clinical and histopathologic assessment of pigmented skin lesions remains challenging even for experts. Differentiated and accurate noninvasive diagnostic modalities are highly desirable.
WHAT IS YOUR DIAGNOSIS?
SPITZOID MELANOMA
Malignant Melanoma w/ Histologic Features of Spitz Nevus

Rare~ 1/500 Spitz Nevus, all ages, more common in Caucasians

3 categories conventional Spitz Nevus, atypical spitzoid tumor, spitzoid melanoma

SN (14 years $♀ > ♂), AST (23 years $♀ = ♂), SM (55 years $♂ > ♀)

Average size at presentation 1.1cm, 51% amelatonic, 30% H&N, 30% EXT's

Overlapping histologic features including epithelioid cells with prominent nucleoli, AST larger lesions typically $> 1.0$ cm, epidermal consumption, loss of kamino bodies, SM epidermal ulceration, ↑ mitoses especially deep

SN (0% sentinel), AST (38%), SM (64%)

CGH/FISH SN (20% gain in 11 p (HRAS) no losses, no more than one alteration, AST (50% variations) 6p25 RRED, 6q23 (MYB), 11q13 (CCND1), 9p21 (INK 4A) SM (96% alteration) 9p21 (homozygous loss), multiple chromosomes gains/losses

Pathogenesis SN(HRAS activation or BAP1 loss or BRAF V600E)

AST(loss of 9p21 w/ loss of p16)
SM (complete loss of 9p21), TERT promoter
<table>
<thead>
<tr>
<th></th>
<th>CONVENTIONAL SPITZ NEVUS</th>
<th>ATYPICAL SPITZOID TUMOR</th>
<th>SPITZOID MELANOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIZE:</td>
<td>0.6CM</td>
<td>1.1CM</td>
<td>1.8CM</td>
</tr>
<tr>
<td>GENDER:</td>
<td>2 ♀:1♂</td>
<td>♀=♂</td>
<td>1♀:2♂</td>
</tr>
<tr>
<td>AGE:</td>
<td>12.1 YEARS</td>
<td>23.2 YEARS</td>
<td>55.1 YEARS</td>
</tr>
<tr>
<td>SYMMETRY:</td>
<td>YES</td>
<td>YES/NO</td>
<td>NO</td>
</tr>
<tr>
<td>ULCERATION:</td>
<td>NO</td>
<td>NO</td>
<td>TYPICALLY YES</td>
</tr>
<tr>
<td>SUBCUTANEOUS FAT</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>KAMINO BODIES:</td>
<td>YES</td>
<td>YES/NO</td>
<td>NO</td>
</tr>
<tr>
<td>ATYPICAL MITOSES</td>
<td>NO</td>
<td>YES/NO</td>
<td>YES</td>
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MELANOCYTIC SUBTYPE
CHROMOSOMAL/GENE ALTERATION

- Melanocytic Subtype
- Spitz Nevus
  - 11p Gain (13%)
- Melanoma
  - 9p Loss (82%), 10 q Loss (63%)
- Acral lentiginous melanoma
  - 1q 32 Loss, 11q 13 Gain
- Mucosal melanoma
  - 1q Gain, 6 p Gain
- Malignant Blue Nevus
  - Oncogene
    - 1p Gain, 4 p Gain, GNAQ
Malignant Melanoma w/ Histologic Features of Spitz Nevus

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THANK YOU!

Questions?