Melanocytic proliferations in sun-damaged skin

Jane L. Messina, MD
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Rare/Unusual Cutaneous Malignancies:
What dermatologists need to know

Jane L. Messina, MD
Senior Member, Departments of Pathology and Cutaneous Oncology
Moffitt Cancer Center
Professor of Pathology and Cell Biology, Dermatology and Cutaneous Surgery and Oncologic Sciences
USF Morsani College of Medicine
75 year old male with rapidly growing nodule
Merkel cell carcinoma

Confirmatory stains:

- Positive: AE1/3 keratin in 100%
- CK20 most specific (88%), perinuclear dots; synaptophysin 92%, chromogranin 84%, NF 80%
- Negative: TTF-1 and CK7
- McPyV detects viral T antigen integrated into genomic: not sensitive (~80%) but specific
- In the rare CK20 negative tumor, McPyV is usually also negative: + NF and SATB2 most useful
- Some tumors show expression of lymphoid markers CD56, Pax5, bcl-2 and Tdt: pre-B-cell origin???
MCC pathogenesis

- Pathogenesis:
  - 20% TP53-driven UV damage pathway
  - 80% MCPyV-driven

- Virus nearly ubiquitous, activated by immunosuppression

- Genomic analysis reveals high tumor mutation burden (TMB) with many UV-signature mutations in virus negative but not virus positive tumors

- Viral status does not have significant correlation with survival

- Viral status did not have significant correlation to immunotherapy response

- Titers of T-antigen correlate with disease status and may predict recurrence (www.merkelcell.org/sero)

Back to our patient: sentinel node 1

AE1/3 keratin
What is the next best course of treatment?

A. Complete node dissection
B. Locoregional XRT
C. Adjuvant systemic therapy
D. More than one of the above

They’re equal!

Management of Sentinel Lymph Node Metastasis in Merkel Cell Carcinoma: Completion Lymphadenectomy, Radiation, or Both?

Matthew C. Perez, MD¹, Daniel E. Oliver, MD², Evan S. Weitman, MD¹, David Boulware, PhD³, Jane L. Messina, MD¹,⁴, Javier Torres-Roca, MD², C. Wayne Cruse, MD¹, Ricardo J. Gonzalez, MD¹, Amod A. Sarnaik, MD¹, Vernon K. Sondak, MD¹, Evan J. Wuthrick, MD¹,², Louis B. Harrison, MD¹,², Jonathan S. Zager, MD¹

¹Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL
²Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL
³Department of Biostatistics, Moffitt Cancer Center, Tampa, FL
⁴Department of Pathology, Moffitt Cancer Center, Tampa, FL
Merkel cell carcinoma: 375 patients at MCC 1988-2011

- Median age: 75 years
- Males: 70%
- Nodal involvement at presentation: 12%
- SLN positivity rate (191 patients): 31%
- Average diameter: 1.5 cm
- Average tumor depth: 4.8 mm

Both predictive of SLN positivity, worse DSS and OS

Radiation improves local control, recurrence, and survival in MCC

- 171 patients with non-metastatic MCC, 2/3 received XRT

Even with negative margins!

Satellitosis in MCC of the auricle

Main tumor mass
NKOTB: Neoadjuvant immunotherapy for MCC

- 39 patients with resectable MCC, Stages IIA-IIIB
- One dose nivolumab 4 weeks before surgery
- Pathologic complete response in 47%: none recurred in 19 months median f/u
- Most useful in setting of:
  - Unresectable primary or recurrent disease
  - Poor surgical candidate
  - Not ready for prime time for primary treatment

PD-L1 and viral status did not show trends for response

67 year old with slowing growing lesion on nose
Sebaceous carcinoma

Best IHC markers: Androgen receptor, adipophilin

Muir-Torre association: Yes

Mismatch repair proteins-to stain or not to stain?
- It’s sensitive! IHC for MLH1, MSH2, MSH6 and PMS are abnormal in ~80% of MTS patients
- Loss of >2 markers has 100% PPV for MTS
- It’s not entirely specific...only 57% in one study

When to stain?

- How many lesions before screening recommended?
  - 60% of MTS patients have one lesion, 30% predate visceral tumors
  - Sebaceous adenoma, epithelioma, carcinoma, NOT hyperplasia

- Which markers?
  - MLH1, MSH2, MSH6, PMS2
  - If one lost, recommend microsatellite instability testing on tissue

- Mayo Risk stratification tool: Score ≥2 had 81% sensitivity and 100% specificity for MTS→IHC

<table>
<thead>
<tr>
<th>Age &lt;60</th>
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<td>&gt;2 lesions</td>
<td>2</td>
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<tr>
<td>Personal history of Lynch associated cancer</td>
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<tr>
<td>Family history of Lynch-associated cancer</td>
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67 year old with “poorly-differentiated SCC” lower abdomen

SCC, squamoid eccrine carcinoma, or porocarcinoma?

EMA highlights ducts
Molecular abnormalities defined by IHC assist in diagnosis of skin adnexal tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>IHC</th>
<th>Clinical implication</th>
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</thead>
<tbody>
<tr>
<td>Pilomatricoma/pilomatrix carcinoma</td>
<td>Beta-catenin, LEF1, CDX2</td>
<td>Lineage-specific</td>
</tr>
<tr>
<td>Trichilemmoma</td>
<td>PTEN</td>
<td>Lost in syndromic tumors only</td>
</tr>
<tr>
<td>Microcystic adnexal carcinoma</td>
<td>pSTAT3</td>
<td>Ddx: syringoma (negative)</td>
</tr>
<tr>
<td>Spiradenocarcinoma/cylindrocarcinoma</td>
<td>P53</td>
<td>Ddx: benign forms (negative)</td>
</tr>
<tr>
<td>Poroid hidradenoma and porocarcinoma</td>
<td>NUT</td>
<td>Lineage-specific, rare in benign poroma</td>
</tr>
<tr>
<td>Mixed tumors (benign and malignant)</td>
<td>PLAG1</td>
<td>Sensitive and specific for dx</td>
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*Figure 4 NUT expression in poroid hidradenoma*
Optimal treatment for adnexal malignancies

• Clinical behavior varies:
  • Width of excision?
  • Role of regional nodal evaluation?
  • Role for radiation therapy?
MCC experience in 103 patients with adnexal malignancies

- Median age 61 years
- 89% Caucasian
- 61% males
- 56% head and neck

Factors influencing survival in adnexal tumors

Size >2 cm and nodal involvement predict worse survival

Nodal involvement most common in porocarcinoma—advocate WLE and SLNB routinely
Optimal treatment for adnexal malignancies

- Clinical behavior varies:
  - Width of excision?
    - 1-2 cm margins, based on functional and anatomic considerations
    - 60% of local recurrences were porocarcinoma or microcystic adnexal carcinoma, 80% recurrent tumors were on head and neck
  - Role of regional nodal evaluation?
    - 10% SLN positivity rate: 1 MAC, 1 apocrine carcinoma
    - Synchronous/metachronous nodal involvement in porocarcinoma and sebaceous carcinoma
  - Role for radiation therapy?
    - Tumor depth, diameter, PNI and LVI did not predict recurrence
    - Remains unclear, consider if complete resection not indicated
- Systemic therapy a complete unknown
65 year with spreading bruise
Atypical cells are CD31, CD34 positive
Cutaneous angiosarcoma—Moffitt experience in 88 patients 1999-2011

• Median age: 70, 57% female
• Tumor size: 3 cm
• 41% received surgery, 47% surgery+XRT
• 76% disease free after treatment, but 50% recurred
• Five-year OS 35%
• Surgery group had highest 5-year OS (47%)


- Head/neck group worst OS
Survival by presentation and therapy

Age <70 years and tumor size <5 cm had less recurrence, better survival
Angiosarcoma—a difficult diagnosis

• CD31 and CD34+ mainstay of diagnosis
  • FLI-1 and Erg
• Most sensitive/specific markers:
  • Lymphatic markers (D2-40, podoplanin) expressed in ~40%
• Epithelial markers EMA, keratins may also be expressed
• Histologic grading does not predict prognosis
• C-myc overexpressed in a subset, portends worse prognosis
Differential c-myc expression in angiosarcoma

Differential diagnosis: atypical vascular lesion

- Arises ~2 years after radiation
- Multifocal, but benign course generally
- 2/27 progressed to angiosarcoma in 25 and 27 months
- In contrast to angiosarcoma, c-MYC negative

44 year old male with mass right shoulder
Dermatofibrosarcoma protuberans

- Second most common dermal sarcoma (KS)
- Young adults (median), trunk>head/neck>extremity
- t(17:22) translocation fuses COL1A1 with PDGFβ, chimeric fusion protein drives tyrosine kinase receptor
- Same abnormality found on:
  - giant cell fibroblastoma of childhood
- 206 patients (MCC and U Michigan): 99% local control with 1-2 cm margins and meticulous pathologic examination (diagram)

En Face Margin Technique

Sections embedded with outer margin “face up”
Recognition of DFSP enhanced by CD34 staining
Fibrosarcomatous DFSP-significance

- Frequency: 5-10%
- Proportion of tumor with FS change did not impact outcome
- CXR should be part of routine followup

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<tr>
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<th>DFSP</th>
<th>DFSP-FS</th>
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<tr>
<td>Local recurrence</td>
<td>13%</td>
<td>30%</td>
</tr>
<tr>
<td>Metastasis (lung, ST)</td>
<td>1%</td>
<td>14%</td>
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<tr>
<td>Death</td>
<td>0.8%</td>
<td>14%</td>
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Dermal sarcoma in sun-damaged skin

- Positive: CD10, vimentin, often SMA and CD68
- Negative: melanocytic, vascular, smooth muscle, and epithelial markers

ATYPICAL FIBROXANTHOMA or PLEOMORPHIC DERMAL SARCOMA?
## Atypical fibroxanthoma v pleomorphic dermal sarcoma

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<thead>
<tr>
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<th>AFX</th>
<th>PDS</th>
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<tr>
<td>IHC</td>
<td>Same</td>
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<tr>
<td>Clinical setting</td>
<td>Head/neck predominance, sun-damaged skin</td>
<td>30% local, 10-25% distant metastasis</td>
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<tr>
<td>Molecular alterations</td>
<td>Frequent UV signature mutations, esp. TP53, TERT promoter</td>
<td></td>
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<tr>
<td>Recurrence</td>
<td>Up to 5%</td>
<td></td>
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<tr>
<td>Histology</td>
<td><img src="image1.jpg" alt="Histology Image" /></td>
<td><img src="image2.jpg" alt="Histology Image" /></td>
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Excellent outcome of atypical fibroxanthoma

- 87 patients with AFX
- 62% required re-excision to establish diagnosis
- Median surgical margin 1.0 cm
- 2.3% local recurrence in 14 month f/u
  - 3 patients recurred, re-excised, reclassified as PDS
- 1 distant recurrence

McClure E, Carr MJ, Patel A et al, manuscript in preparation
Beyond melanoma and keratinocyte cancer...

Clinical presentation, diagnostic pearls, treatment and outcome of

• Merkel cell carcinoma
• Adnexal malignancies
• Cool cutaneous sarcomas