Diagnostic Challenges with Epithelial Tumors

KJ Busam, MD
Diagnostic Challenges with Sweat Gland Carcinomas

• Is a tumor benign or malignant (or uncertain)

• Is the tumor a primary skin cancer or a metastasis?

• If primary carcinoma, what is the risk for recurrence?
  • Conservative vs wide excision
  • Sentinel lymph node biopsy

• Is the carcinoma of sweat gland or other cutaneous origin
## Basic Approach: Benign or Malignant

<table>
<thead>
<tr>
<th>Adenoma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Circumscribed</td>
<td>• Infiltrative</td>
</tr>
<tr>
<td>• Cytologically bland</td>
<td>• Cytologically atypical</td>
</tr>
<tr>
<td>• Cell elements</td>
<td>• Cell elements</td>
</tr>
<tr>
<td>• Duct epithelial surrounded by myoepithelial cells</td>
<td>• Ductal carcinomas: No myoepithelial cells = carcinoma</td>
</tr>
<tr>
<td>• Myoepithelial cells may dominate</td>
<td>• Caution: Some carcinomas have epithelial and myoepithelial cells</td>
</tr>
</tbody>
</table>
Ductal vs Epithelial/Myoepithelial Carcinoma

Ductal Carcinomas

• Ductal carcinoma, NOS
• Mucinous carcinoma
• Cribriform carcinoma
• Secretory carcinoma

Epithelial – Myoepithelial Carcinomas

• Adenoid cystic carcinoma
• Malignant mixed tumor
• Cylindro/spiradenocarcinoma
• Digital papillary adenocarcinoma

The Utility of Myoepithelial Cell Layer Identification in Adnexal Carcinomas

Jose A. Plaza, MD,* Catherine Chung, MD,† Mark Wick, MD,‡ Martin Sangueza, MD,§ and Alejandro Gru, MD,**
Basic Approach: Risk for Metastasis

Low or none

- Cribriform carcinoma
- Endocrine MP-carcinoma
- Pure mucinous carcinoma
- MAC

Risk for metastasis

- Porocarcinoma
- Hidradenocarcinoma
- Cylindro/spiradenocarcinoma
- EMPD, invasive
- Mixed mucinous carcinoma
- Digital papillary adenocarcinoma
**Basic Approach:** Is there a precursor or not?

<table>
<thead>
<tr>
<th>Adenoma-associated</th>
<th>De Novo</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Carcinoma ex cylindroma</td>
<td>• Mucinous carcinoma</td>
</tr>
<tr>
<td>• Carcinoma ex spiradenoma</td>
<td>• Endocrine mucin-prod. carcinoma</td>
</tr>
<tr>
<td>• Carcinoma ex hidradenoma</td>
<td>• Papillary Digital Adenocarcinoma</td>
</tr>
<tr>
<td>• Carcinoma ex poroma</td>
<td>• Cribriform carcinoma</td>
</tr>
<tr>
<td>• Carcinoma ex mixed tumor</td>
<td>• Adenoid cystic carcinoma</td>
</tr>
</tbody>
</table>
Adenocarcinoma in Subcutis
Carcinoma ex Spiradenoma (Spiradenocarcinoma)
What is Your Diagnosis?
Porocarcinoma (carcinoma a/w poroma)
Molecular Approach – Gene Fusions

Table 2. Summary of the most frequent molecular alterations in sweat gland neoplasms.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Molecular Alteration</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>MYB-NFIB fusion</td>
<td>73–83%</td>
</tr>
<tr>
<td></td>
<td>MYBL1-NFIB fusion</td>
<td>20–23%</td>
</tr>
<tr>
<td>Cutaneous mixed tumor</td>
<td>PLAG1 fusion</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>HMGA2 fusion</td>
<td>unknown</td>
</tr>
<tr>
<td>Cylindroma</td>
<td>CYLD inactivation</td>
<td>near 100%</td>
</tr>
<tr>
<td>Spiradenoma</td>
<td>CYLD inactivation</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>ALPK1 p.V1092A mutation</td>
<td>43%</td>
</tr>
<tr>
<td>Spiradenocarcinoma</td>
<td>CYLD inactivation</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>ALPK1 p.V1092A mutation</td>
<td>33%</td>
</tr>
<tr>
<td>Hidradenoma</td>
<td>CRTCl-MAML2 fusion</td>
<td>50–75%</td>
</tr>
<tr>
<td></td>
<td>CRTCl-MAML2 fusion</td>
<td>rare</td>
</tr>
<tr>
<td>Hidradenocarcinoma</td>
<td>CRTCl-MAML2 fusion</td>
<td>unknown</td>
</tr>
<tr>
<td>Myoepithelioma</td>
<td>EWSRT fusion</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>FUS fusion</td>
<td>18%</td>
</tr>
<tr>
<td>Poroma</td>
<td>YAPI fusion</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>NUTM1 fusion</td>
<td>17–55%</td>
</tr>
<tr>
<td>Porocarcinoma</td>
<td>YAPI fusion</td>
<td>8–63%</td>
</tr>
<tr>
<td></td>
<td>NUTM1 fusion</td>
<td>11–54%</td>
</tr>
<tr>
<td>Secretory carcinoma</td>
<td>ETV6-NTRK3 fusion</td>
<td>near 100%</td>
</tr>
<tr>
<td>Syringocystadenoma papilliferum and tubular adenoma</td>
<td>BRAF p.V600E mutation</td>
<td>50–64%</td>
</tr>
<tr>
<td></td>
<td>HRAS p.G13R mutation</td>
<td>7–26%</td>
</tr>
<tr>
<td></td>
<td>KRAS p.G12D mutation</td>
<td>rare</td>
</tr>
</tbody>
</table>
Exploring Diagnostic Opportunities

Recurrent YAP1-MAML2 and YAP1-NUTM1 fusions in poroma and porocarcinoma
Shigeki Sekine,1,5 Tohru Kiyono,1,4 Eiji Tsuka,2 Reiko Ogawa,2 Susumu Wataki,1 Hitoshi Ichikawa,1 Kenji Suzuki,3,9 Satoru Arai,2 Koji Tsuta,9 Mitsuoaki Ishida,9 Yuki Sasaajima,9 Naoki Goshima,10 Naoya Yamazaki,11 and Taisuke Mori1,2

Utility of YAP1 and NUT immunohistochemistry in the diagnosis of porocarcinoma
Eleanor Russell-Goldman | Jason L. Hornick | John Hanna

Limited Sensitivity and/or Specificity

MYB, CD117 and SOX-10 expression in cutaneous adnexal tumors
Mara Therese P. Evangelista | Jeffrey P. North
Porocarcinoma with YAP1::NUTM1 Fusion
CASE STUDY

Spindle cell porocarcinoma with a novel YAP1::MAML3 fusion

Philippa Li MD¹ | Klaus J. Busam MD²
Secretory Carcinoma

Variant of apocrine carcinoma
- Breast
- Salivary Gland
- Skin
- Other
Secretory Carcinoma
Secretory Carcinoma – Gene Fusions
Secretory Carcinoma

Generally reported as “indolent” carcinoma


Secretory Carcinoma
Metastatic Secretory Carcinoma
Microsecretory Carcinoma

Microsecretory adenocarcinoma of the skin harboring recurrent SS18 fusions: A cutaneous analog to a newly described salivary gland tumor

Justin A. Bishop | Erik A. Williams | Anne C. McLean | Jeffrey Gagan
Lisa M. Rooper | Richard C. K. Jordan | Philip E. LeBoit

09/2018 08/2020
Microsecretory Carcinoma - Pathology
Hyalinizing Clear Cell Carcinoma

72M, nose
Hyalinizing Clear Cell Carcinoma

Molecular: EWSR1-ATF1
Ductal vs Epithelial/Myoepithelial Carcinoma

**Ductal Carcinomas**

- Ductal carcinoma, NOS
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- Secretory carcinoma

**Epithelial – Myoepithelial Carcinomas**

- Adenoid cystic carcinoma
- Malignant mixed tumor
- Cylindrocarcinoma
- Digital papillary adenocarcinoma
Digital Papillary Adenocarcinoma (DPAC)
DPAC – Basic Facts

• Incidence: 0.08 per 1,000,000
• Median age at diagnosis: 50
• Men: Women = 4:1
• Predilection for digits and toes
• Risk for metastasis: approx. 15%
• Treatment: Surgical resection
21M with mass on rt 5th finger
Digital Papillary Adenocarcinoma
Metastatic Digital Papillary Adenocarcinoma
DPAC – A Diagnostic Challenge

“Apocrine Hidrocystoma and Cystadenoma”–like Tumor of the Digits or Toes
A Potential Diagnostic Pitfall of Digital Papillary Adenocarcinoma

Ana-Maria Molina-Ruiz, MD,* Mar Llamas-Velasco, MD,† Arno Rütten, MD,‡ Lorenzo Cerroni, MD,§ and Luis Requena, MD*

Clinicopathologic Characterization of Hidradenoma on Acral Sites
A Diagnostic Pitfall With Digital Papillary Adenocarcinoma

Katharina Wiedemeyer, MD,*† Pavandeep Gill, MD,* Michelle Schneider, MD,* Peter Kind, MD,‡ and Thomas Brenn, MD, PhD, FRCPath*§‖

Can be confused with a benign sweat gland tumor
DPAC - History

• Helwig in 1984: “aggressive papillary adenoma”

• Kao in 1998: series of “aggressive papillary digital adenoma” and “aggressive papillary digital adenocarcinoma”

• Duke in 2000:
Sentinel lymph node biopsy predicts systemic recurrence in digital papillary adenocarcinoma

Meredith K. Bartelstein MD1 | Eugenia Schwarzkopf MD2 | Klaus J. Busam MD3 | Mary Sue Brady MD3 | Edward A. Athanasian MD3

1Department of Surgery, Orthopaedic Service, Memorial Sloan Kettering Cancer Center, New York, New York
2Department of Surgery, Emory University, Atlanta, Georgia
3Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York

Abstract

Background and Objectives: Digital papillary adenocarcinoma (DPA) is a rare, aggressive neoplasm of sweat gland origin. It can recur at local, regional, or distant sites. There is limited knowledge about the role of sentinel lymph node biopsy (SLNB) in predicting recurrence in these patients. We present our experience with this uncommon tumor to evaluate the role of SLNB in predicting outcome.

Methods: Medical records of all patients who underwent surgical treatment for biopsy-proven upper extremity DPA at the study institution were reviewed. Descriptive statistics and Fisher’s exact test were used to analyze data.

Results: Twenty-one patients were identified. Most patients were male (71%), and the median age was 51 years. SLNB was performed in 18 patients; three were positive for nodal metastatic disease (17%). At a median follow-up of 53 months, there were no local recurrences and two cases of systemic recurrence. No patient with a negative sentinel lymph node had evidence of metastasis or recurrence. Fisher’s exact test demonstrated a significant association between a positive SLNB and recurrence (P = .02).

Conclusions: SLNB revealed metastatic disease in 17% of patients with DPA and appears to predict systemic recurrence in this small series.

- 21 patients, 71% men, median age 51
- 17% had a pos SLN
- 2/21 had distant mets
- None of the patients with neg SLN had distant recurrence
Mutations said to be associated with DPAC

  • NGS: 1/9 cases with *BRAFV600E* mutation

  • Single case report with *BRAFV600E* mutation
Report of BRAF Mutation in “DPAC”

1 of 9 tumors with 
BRAFV600E

UNUSUAL CASE
- 31F
- Ankle
- NED (1yr)
Report of BRAF Mutation in “DPAC”

A Case Report of Papillary Digital Adenocarcinoma With BRAFV600E Mutation and Quantified Mutational Burden

Megan H. Trager, BA,* Magdalena Jurkiewicz, MD, PhD,† Shaheer Khan, MD,‡ George W. Niedt, MD,§ Larisa J. Geskin, MD,¶ and Richard D. Carvajal, MD∥

- 63 yo woman
- Right forearm
- “High TMB”
Tubulopapillary Adenomas harbor BRAF mutations

BRAFV600E Mutation:
- 9/15 (60%) of TAA
- 7/8 (78%) of PEA
Next Generation Sequence Analysis of Tumors

• Searching for point mutations

• Searching for gene fusions

• Also permits search for potential non-human pathogens
NGS to Detect Virus-Tumor Associations

Chad Vanderbilt and colleagues

Thomas Wiesner and colleagues
Hybridization capture library enrichment

Image adapted from Duncavage et al. JMD. 2011
Off-targets enable identification of microorganisms.
Bioinformatics Process

- 60,000 MSK-IMPACT Cases
- FASTQ Files
- Alignment (BWA)
- Post-Processing (GATK)
- Extract Unmapped Reads
- BLASTN alignment
- Species level Microbe identification
- Database of microbe Genomes
- Tumor-Normal BAM Generation
- Variant Calling Modules
- Oncogenic variants annotated via OncoKB

Oncogenic variants annotated via OncoKB

Database of microbe Genomes

60,000 MSK-IMPACT Cases

FASTQ Files

Alignment (BWA)

Post-Processing (GATK)

Extract Unmapped Reads

BLASTN alignment

Species level Microbe identification

Tumor-Normal BAM Generation

Variant Calling Modules

Oncogenic variants annotated via OncoKB
Sequence Analysis Detects HPV42 in DPAC

• 55,000 cases analyzed by MSK-IMPACT

• 4 skin tumors positive for HPV42

• All had been diagnosed as DPAC
HPV42 Detection in Metastatic DPAC
## Acral Sites

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Anatomic Site</th>
<th>Size (mm)</th>
<th>Growth</th>
<th>ISH HPV42</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>rt 3rd finger</td>
<td>17</td>
<td>nodular</td>
<td>POSITIVE</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>M</td>
<td>rt 2nd finger</td>
<td>8</td>
<td>nodular</td>
<td>POSITIVE</td>
<td>LN, ST</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>M</td>
<td>rt 2nd finger</td>
<td>30</td>
<td>infiltrative</td>
<td>POSITIVE</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>M</td>
<td>rt 3rd finger</td>
<td>5</td>
<td>nodular</td>
<td>POSITIVE</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>M</td>
<td>rt 4th toe</td>
<td>13</td>
<td>nodular</td>
<td>POSITIVE</td>
<td>LN (4/10)</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>M</td>
<td>rt great toe</td>
<td>20</td>
<td>nodular</td>
<td>POSITIVE</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>M</td>
<td>rt 5th finger</td>
<td>18</td>
<td>nodular</td>
<td>POSITIVE</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>M</td>
<td>lt thumb</td>
<td>16</td>
<td>nodular</td>
<td>POSITIVE</td>
<td>LN</td>
</tr>
</tbody>
</table>

## Non-Acral Sites

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Anatomic Site</th>
<th>Size (mm)</th>
<th>Growth</th>
<th>ISH HPV42</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>80</td>
<td>M</td>
<td>scrotum</td>
<td>20</td>
<td>nodular</td>
<td>POSITIVE</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>77</td>
<td>M</td>
<td>scrotum</td>
<td>8</td>
<td>nodular</td>
<td>POSITIVE</td>
<td></td>
</tr>
</tbody>
</table>
Association of HPV42 with digital papillary adenocarcinoma and the use of in situ hybridization for its distinction from acral hidradenoma and diagnosis at non-acral sites

Chad Vanderbilt, Thomas Brennan, Andrea P. Moy, Gordon Harloe, Charlotte Aryan, Edward Athanasian and Klaus J. Busam

Digital Papillary Adenocarcinoma in Nonacral Skin
Clinicopathologic and Genetic Characterization of 5 Cases
Thibault Kervarrec, MD, PhD,**†† Sandrine Imbeaud, PhD,§ David Veyer, PharmD, PhD,§§ Helene Pereg, PharmD, PhD,¶¶ Julien Puech,§ Agnes Pekár-Liska, MD,¶¶ Dorota Markiewicz, MD,# Michael Couats, MD,** Anne Tallet, PharmD,†† Christine Collin, PhD,†† Patricia Berthon, PhD,† Ignacio G. Bravo, PhD,‡‡ Alice Seris,‡‡ Thomas Jouary, MD,§§ Nicolas Macagno, MD, PhD,¶¶¶ Antoine Touzé, PhD,‡‡ Bernard Cribier, MD, PhD,### Maxime Battistella, MD, PhD,### and Eduardo Calonje, MD#
Potential Utility of ISH for HPV42

• Diagnosis of poorly differentiated primary DPAC

• Diagnosis of well-differential adenoma-like DPAC

• Diagnosis of DPAC at non-acral sites

• Diagnosis of metastatic DPAC
What is Your Diagnosis?

68 M with axillary mass
What is Your Diagnosis?

68 M with axillary mass
What is Your diagnosis?

A. Adenoid cystic carcinoma

B. Spiradenocarcinoma

C. Cylindrocarcinoma

D. Other
Metastatic DPAC
Clinical History

• Prior diagnosis of "benign" eccrine tumor in 2008; narrowly excised

• Recurred in 2010; excised with negative margin

\textit{Final Anatomic Diagnosis}

1. THUMB, SOFT TISSUE, LEFT
   Eccrine Acrosiroma (Eccrine Nodular Hidradenoma)
   FROZEN SECTION DIAGNOSIS: Epithelial lesion. Wait for permanent section for further classification (Dr. M. Bansal)
2. THUMB, SOFT TISSUE, LEFT
   Eccrine Acrosiroma (Eccrine Nodular Hidradenoma)

\textit{Comment on Case}

Although eccrine acrosiromas are benign tumors which do not exhibit a high rate of recurrence, close clinical follow-up is recommended due to the marginal excision of the tumor and the lack of clear margins of resection.
Biopsy from 2008
DPAC – Positive for HPV42
Digital Papillary Adenocarcinoma

- Scientific advances have helped improve the classification of sweat gland carcinoma

- DPAC can be confused with other sweat gland tumors

- HPV42 is associated with DPAC

- In situ hybridization of HPV42 can help support the diagnosis of DPAC and distinguish it from histologic mimics
Virus-Associated Malignant Solid Skin Tumors

- Squamous cell carcinoma (HPV)
- Kaposi sarcoma (HHV8)
- Merkel cell carcinoma (MCPyV)
- DPAC (HPV42)
ISH for HPV42 helps to recognize DPAC

- Poroma
- Hidradenoma
- Cystadenoma
- Cylindroma
- Tubulopapillary adenoma

HPV42
HPV42-associated SK-like lesion
Adenocarcinoma - primary or metastatic?

• Is there an associated adenoma?

• Does the carcinoma have distinct features that reveal its stage?

• Does the patient have a history of prior carcinoma?
Primary neoplasm or metastatic?
Metastasis with Distinct IHC

Metastatic Thyroid Carcinoma
What is Your Diagnosis?

76M
Scalp
What is Your Diagnosis?
CLINICAL INFORMATION:
A. SKIN. Right vertex scalp: Patient with hepatocellular carcinoma and 1 cm exophytic white dermal nodule of unclear duration on right vertex of scalp. I expected cyst but it is not cystic shelled out DDX: CARTILAGINOUS MIXED TUMOR/ECCrine? PEN/SCHWANNOMA. D48.5 - Please check margins

DIAGNOSIS:
A. SKIN. Right vertex scalp:
-MODERATELY DIFFERENTIATED ADENOCARCINOMA, POSSIBLY REPRESENTING AN ADENOCARCINOMA, ARISING IN A PRE-EXISTING CHONDROID SYRINGOMA/MIXED TUMOR.
Diagnosis: Metastatic Cholangiocarcinoma

**CYTOLOGIC DIAGNOSIS:**
Work-up of Adenocarcinoma in Dermis

• Clinical history is paramount

• Review of entire tumor may provide clues (e.g., associated adenoma)

• Ancillary studies can help, but not always

• Tumors with features that do not fit a known entity may be mets

• Comparative pathology (H&E, IHC, molecular) is important
Mucinous Carcinoma
Primary Cutaneous Mucinous Carcinoma
Mucinous Carcinoma - Cytology
Mixed Mucinous Carcinoma
Mucinous Carcinoma

• First report by Lennox et al J Pathol Bacteriol 1952; 74: 865-80

• Requena&Sangueza (Cutaneous Adnexal Neoplasms; Springer, 2017):
  • Reviewed 287 cases of reported mucinous carcinoma
  • 80% of patients are between 50-60 yrs of age
  • Predilection for head and neck area, especially eyelids
  • Associated metastases
    • 21/287 (7.3%) with regional LN metastasis
    • 9/287 (3.1%) with distant metastasis
Mucinous Carcinoma – Primary vs Metastatic

• Requena & Sangueza in Cutaneous Adnexal Neoplasms, 2017; p326:
  • “The majority of the mucinous carcinomas involving the skin are metastatic”
  • “In any patient with mucinous ca of the skin, it is important to r/o metastasis”

• MSKCC Experience
  • Pure “low grade” mucinous carcinomas tend to be primary cutaneous
  • Most metastatic carcinomas to the skin are mixed mucinous carcinomas or adenocarcinomas with mucinous features
Mucinous (Colloid) Mammary Carcinoma

MSKCC Experience

- 849 patients with mucinous mammary carcinoma
- 159 metastasized (15%)
- Most common sites of metastasis
  - Lung
  - Lymph node
- First metastasis to skin very rare
Mixed Mucinous Carcinoma

Stroma-Rich, Cell-Poor

Stroma-Poor, Cell-Rich
Metastasizing Mucinous Mammary Carcinoma
Metastatic AdenoCA with Mucinous Features
Mucinous Signet Ring Cell Carcinoma

Metastatic Colorectal Signet Ring Cell Carcinoma
Primary Cutaneous Mucinous Carcinoma
Endocrine Mucin-Producing Sweat Gland Carcinoma
Endocrine Mucin-Producing Sweat Gland Carcinoma

- **Clinical**
  - Typically periocular
  - Low grade neoplasm

- **Histopathology**
  - Intra- and peritumoral mucin
  - Solid and cribriform growth
  - Low nuclear grade

- **IHC**
  - CK7, ER, PR, INSM1, chromo, synaptophysin
What is Your Diagnosis?

- 75F with scalp nodule
- R/o cyst
What is Your Diagnosis?

A. Endocrine mucin-producing sweat gland carcinoma

B. Primary mucinous carcinoma of the skin

C. Metastatic adenocarcinoma with mucinous features
Mammary Carcinoma
Challenging Case – Primary or Metastatic?

- History of breast cancer, metastatic to LNs
- S/p chemo, XRT + tamoxifen
- Dark fleck along right lateral eye
- Dermatologist took 1 mm punch biopsy x2:
  - Prelim report: foreign body reaction
  - Addendum: c/w metastatic breast cancer
Outside Pathology Report

Clinical Information
Morphology: linear bluish grey dermal macule
DDX: Neoplasm of uncertain behavior vs melanoma
Notes: 2 pieces

Final Diagnosis
Skin, right lateral canthus, punch biopsy
- Consistent with metastatic mammary carcinoma. See note

Note: The neoplastic cells show strong immunoreactivity with AE1.3 and GATA 3. There is also focal positive staining with ER. Patient's past medical history of a lobular carcinoma is also noted.

Polarizable foreign material and nonpolarizable pigmented foreign material present. Initial and deeper sections have been analyzed. PAS stain fails to reveal fungal elements. AFB stain fails to reveal mycobacteria. The atypical cells are negative for S-100, HMB45, CD68, TTF1, PAX 8 and Melan A.
Pathology

Right lateral canthus
Poorly differentiated carcinoma

CKAE1/3
Right lateral canthus; Keratin (AE1/AE3)
Poorly differentiated carcinoma
DIAGNOSIS:
1. Skin, right lateral canthus; punch biopsy
   - Poorly differentiated carcinoma. See note

Note: The submitted IHC stains show the carcinoma cells positive for AE1/3 and GATA3, while negative for PAX8, melan-A and ER. S100 and CD68 show non-specific staining. In the context of the patient’s history of invasive lobular carcinoma, this may represent metastatic lobular carcinoma when other primary sites have been excluded.
What is Your Diagnosis?

A. Metastatic mammary carcinoma

B. Primary sweat gland carcinoma

C. Poorly differentiated sebaceous carcinoma

D. Metastatic carcinoma from another site

E. Other
What is the next best step?

A. Chemotherapy

B. Additional immunostains for TTF1, GATA3, Pax8, Other

C. Test for ER, PR, Her2Neu

D. Genetic test to determine anatomic site of origin

E. Other
Clinical History

• Patient seen by Breast Onc survivorship
• Started on Letrozole (Femara)
• Sent to Derm for exc of breast met
• Clinically, no lesion left
Next best step – further diagnostic work-up

• Review prior mammary carcinoma for comparison

• Re-review slides and pathology reports

• Consider additional tumor tissue sampling for further analysis
Pathology

Right lateral canthus
Poorly differentiated carcinoma

CKAE1/3
What is wrong with this picture?
Outside Pathology Report

Clinical Information
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Gross Description
The specimen is received in formalin and the specimen container is labeled: Right lateral canthus. It consists of two minute skin punches biopsies each measuring 0.1 x 0.1 cm. in diameter and taken to a depth of 0.1cm. The epidermis is tan-white and soft. The specimen is entirely submitted in one cassette.
Gross Description

The specimen is received in formalin and the specimen container is labeled: **Right lateral canthus**. It consists of **two minute skin punch biopsies** each measuring 0.1 x 0.1 cm. in diameter and taken to a depth of 0.1 cm. The epidermis is tan-white and soft. The specimen is entirely submitted in one cassette.
Punch biopsy
What is wrong?

There are 3 pieces!!
Where does the 3rd big piece come from?
Excisional biopsy: no tumor seen
Molecular Tests for Specimen ID

MOLECULAR RESULTS.

1) Malignant tissue present in the 2018 right canthus tissue specimen. Autosomal microsatellite markers: A profile of polymorphic microsatellite markers located at 1p36, 1p34, 3p, 5q, 17p, 17q and 18q.

Amelogenin gender marker: Male

2) 2018 non-neoplastic squamous epithelium from the right lateral canthus. Autosomal microsatellite markers: A completely non-matching profile of polymorphic microsatellite markers located at 1p36, 1p34, 3p, 5q, 17p, 17q and 18q compared to the malignant tissue in part 1) above (see comment).

Amelogenin gender marker: Female
Primary or Metastatic Carcinoma?

No carcinoma at all
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busamk@mskcc.org