Cutaneous adnexal tumors – What’s new?

Meera Mahalingam, MD, PhD, FRCPath

Age-adjusted IR 5.1/million person years

IR increased 100 fold with age

37.3

0.37
Part I

New Entities

- Endocrine mucin-producing sweat gland carcinoma
- Primary cutaneous cribriform carcinoma
- Squamoid eccrine ductal carcinoma

“Monocle” tumor

Endocrine Mucin-Producing Sweat Gland Carcinoma

Am J Surg Path. 2005
Defining histopathology

- Well-circumscribed single or multiple tumor lobules in the dermis with solid, cystic and papillary growth patterns
- Bland cytology
- Extracellular mucin
EMSGC
Clarification of nomenclature

- Rare, low-grade sweat gland carcinoma, which is morphologically analogous to solid papillary carcinoma of the breast.
- Considered to be in the spectrum of cutaneous mucinous neoplasms and a precursor of primary cutaneous mucinous carcinoma.
Endocrine Mucin-Producing Sweat Gland Carcinoma
Twelve New Cases Suggest That It Is a Precursor of Some Invasive Mucinous Carcinomas

Mimic 1 - BCC
Mimic 2 - Spiradenoma

Mimic 3 – Chondroid syringoma

Dual cell population

Mucinous stroma

Eosinophilic cuticle droplets

Bland

Dermal

Chondroidal stroma

Bland

Dermal
EMPSGC

Take home points

- 50% of endocrine mucin-producing sweat gland carcinomas in one series was associated with mucinous carcinoma suggesting that it is a precursor to some mucinous carcinomas
- A limited biopsy showing only the cystic component may very easily be mistaken for something else...

New “ish” Entities

- Endocrine mucin-producing sweat gland carcinoma
- Primary cutaneous cribriform carcinoma
- Squamoid eccrine ductal carcinoma
More recent series....

Primary cutaneous cribiform carcinoma: report of six cases with clinicopathologic data and immunohistochemical profile.

Biologic behavior

Table 1: Clinicopathologic characteristics of PCCC reported in the literature and in this study

<table>
<thead>
<tr>
<th>Sex (number of cases)</th>
<th>Average age (range)</th>
<th>Location</th>
<th>Available follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (10)</td>
<td>52 years (50-68)</td>
<td>Head</td>
<td>3 cases with no recurrence or metastases after resection.</td>
</tr>
<tr>
<td>F (8)</td>
<td>47 years (29-68)</td>
<td>Scalp</td>
<td>12 cases with no recurrence or metastases after resection.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53 years (35-59)</td>
<td>Head</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51 years (40-62)</td>
<td>Scalp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 years (21-30)</td>
<td>Scalp</td>
</tr>
</tbody>
</table>

Table 2: Immunohistochemical profile of primary cutaneous cribiform carcinoma (PCCC) with factor antibodies (ab)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>PCCC</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100</td>
<td>+</td>
<td>90</td>
</tr>
<tr>
<td>C-Kit</td>
<td>+</td>
<td>90</td>
</tr>
<tr>
<td>SMA</td>
<td>+</td>
<td>90</td>
</tr>
<tr>
<td>CD34</td>
<td>+</td>
<td>90</td>
</tr>
<tr>
<td>CK7</td>
<td>+</td>
<td>90</td>
</tr>
<tr>
<td>CK10</td>
<td>+</td>
<td>90</td>
</tr>
<tr>
<td>CK14</td>
<td>+</td>
<td>90</td>
</tr>
<tr>
<td>CK20</td>
<td>+</td>
<td>90</td>
</tr>
<tr>
<td>CK70</td>
<td>+</td>
<td>90</td>
</tr>
</tbody>
</table>
**Mimic 1 – Tubular adenoma**

**PCCC**
Tubular adenoma

PCCC - Calponin

Mimic 2 – Adenoid cystic carcinoma

Table III: Histopathologic differential diagnosis between primary cutaneous adenoid cystic carcinoma and primary cutaneous cribriform apocrine carcinoma

- Primary cutaneous cribriform apocrine carcinoma
  - Cribriform pattern throughout entire neoplasm
  - Neoplastic aggregations varied in size and shape
  - Neoplastic aggregations interconnecting
  - Spaces within aggregations varied in size and shape
  - Autocrine stimulated tubules
  - No deposits of basement membrane material
  - Phospho-erotic nuclei of neoplastic cells
  - No neuronomes
New “ish” Entities

- Endocrine mucin-producing sweat gland carcinoma
- Primary cutaneous cribriform carcinoma
- Squamoid eccrine ductal carcinoma

Other names

- Adenosquamous carcinoma
- Ductal eccrine carcinoma with squamous differentiation
- Squamoid variant of microcystic adnexal carcinoma
up to 50% of all eccrine carcinomas (in comparison with 0.5% of squamous cell carcinomas) metastasize.
Squamous Eccrine Ductal Carcinoma
A Clinicopathologic Study of 30 Cases

Markish P.L., van der Horst, MD*; Adeosua Gbadebo-Emeoma, MD; Dorota Markowska; MD†;
Bernice M. Mancini, MD FAPRCPath; Galen A. Gallo; MD, FAPRCPath; and
Thomas Bento, MD, FAPRCPath


Last week.....
Sclerosing neoplasms

<table>
<thead>
<tr>
<th>Age in years</th>
<th>56</th>
<th>47</th>
<th>81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization</td>
<td>Periocular area</td>
<td>Cheek</td>
<td>Cheek</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Cysts, Strands, PNI</td>
<td>Strands, PNI</td>
<td>Keratinization, LVI, PNI</td>
</tr>
<tr>
<td>IHC</td>
<td>PHLDA1+</td>
<td>PHLDA1+</td>
<td>PHLDA1+ only in deeper portion</td>
</tr>
</tbody>
</table>

**Part II**

**Adnexal neoplasms and IHC**

**What to use and when?**
BCC vs trichoepithelioma

BCC - Androgen receptor

BCC - CK20

BCC vs trichoepithelioma

Recommended panel

MAC? Other sclerosing neoplasm?
MAC vs other sclerosing neoplasms

**Recommended panel**

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>MAC, %</th>
<th>dTE, %</th>
<th>infiltrative BCC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK5</td>
<td>92</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>CD44</td>
<td>3–100 (ducts)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CK7</td>
<td>15</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>BerEP44</td>
<td>0–38</td>
<td>57–75</td>
<td>100</td>
</tr>
<tr>
<td>CD68</td>
<td>31</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>CD123</td>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P53</td>
<td>100 (peripheral, deep)</td>
<td>100</td>
<td>—</td>
</tr>
<tr>
<td>P75</td>
<td>—</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>AR</td>
<td>—</td>
<td>13</td>
<td>65</td>
</tr>
<tr>
<td>CK20+ Merkel cells</td>
<td>0</td>
<td>100</td>
<td>0.9</td>
</tr>
<tr>
<td>CD5</td>
<td>71 (deep)</td>
<td>38</td>
<td>15</td>
</tr>
</tbody>
</table>

**Porocarcinoma? SCC?**

**Table 3: Summary of immunohistochemical studies**

- **Cytokeratin 8**:
  - 95% (100% in ducts)
  - 100% (90% in ducts)
- **Cytokeratin 19**:
  - 95% (100% in ducts)
  - 100% (90% in ducts)
- **Cytokeratin 20**:
  - 95% (100% in ducts)
  - 100% (90% in ducts)
- **Cytokeratin 7**:
  - 95% (100% in ducts)
  - 100% (90% in ducts)
- **Cytokeratin 5**:
  - 95% (100% in ducts)
  - 100% (90% in ducts)
- **Cytokeratin 19**:
  - 95% (100% in ducts)
  - 100% (90% in ducts)
- **Cytokeratin 20**:
  - 95% (100% in ducts)
  - 100% (90% in ducts)
- **Cytokeratin 7**:
  - 95% (100% in ducts)
  - 100% (90% in ducts)
Porocarcinoma vs SCC

Recommended panel

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>Porocarcinoma, %</th>
<th>SCC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK15</td>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>CEA</td>
<td>100 + ducts</td>
<td>20–80</td>
</tr>
<tr>
<td>CK7</td>
<td>—</td>
<td>13–22</td>
</tr>
<tr>
<td>EMA</td>
<td>94–100</td>
<td>85–100</td>
</tr>
<tr>
<td>Nestin</td>
<td>35</td>
<td>—</td>
</tr>
<tr>
<td>CD15</td>
<td>10</td>
<td>0</td>
</tr>
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</table>
Perforin expression in eyelid sebaceous carcinomas: a useful and specific immunomarker for the differential diagnosis of eyelid carcinomas

**Perforin expression in eyelid sebaceous carcinomas: a useful and specific immunomarker for the differential diagnosis of eyelid carcinomas**

**Sebaceous carcinoma vs SCC**

**Recommended panel**

<table>
<thead>
<tr>
<th>BerEP4</th>
<th>Adipophilin</th>
<th>Perforin</th>
<th>EMA</th>
<th>CD5</th>
</tr>
</thead>
<tbody>
<tr>
<td>BerEP4</td>
<td>10-80</td>
<td>3-10</td>
<td>10-80</td>
<td>10-80</td>
</tr>
<tr>
<td>Adipophilin</td>
<td>10-80</td>
<td>3-10</td>
<td>10-80</td>
<td>10-80</td>
</tr>
<tr>
<td>Perforin</td>
<td>10-80</td>
<td>3-10</td>
<td>10-80</td>
<td>10-80</td>
</tr>
<tr>
<td>EMA</td>
<td>10-80</td>
<td>3-10</td>
<td>10-80</td>
<td>10-80</td>
</tr>
<tr>
<td>CD5</td>
<td>10-80</td>
<td>3-10</td>
<td>10-80</td>
<td>10-80</td>
</tr>
</tbody>
</table>

Sebaceous carcinoma: an immunohistochemical reappraisal.

The list of BerEP4 and Adipophilin is sebaceous carcinomas (SC) have been reported to be higher than those of other tumours, such as squamous cell carcinomas (SCC) and basal cell carcinomas (BCC), regardless of whether they occur in sebaceous or non-sebaceous regions. Therefore, the differentiation of SCC from BCC and SCC is important in the clinical setting. The results also show that BerEP4 and Adipophilin expression are useful and specific immunomarkers for the differential diagnosis of eyelid carcinomas.
Sebaceous neoplasms & Muir-Torre syndrome

Pts with unselected sebaceous neoplasms

- Sebaceous adenoma, epithelioma, or carcinoma

- Site: Below head and neck
  - Age < 50 years

- Immunohistochemical analysis (MSH6, MSH2, MLH1)
  - Positive (lack of one/more MMRs)
  - Negative (No lack of MMRs)

- Positive MSI analyses
- Negative MSI analyses

- Positive family history
- Negative family history

- No further work-up required
- Further work-up required

- Strict cancer surveillance for proband and family members at risk

Mismatch repair proteins

MSH2  MLH1

Mismatch repair proteins (MSH2, MLH1)

Modern Pathology, 2008

**MSH6 syndrome**

Jerome Sutcliffe, Brian Lomax

Corresponding author: Jerome Sutcliffe, International Breast Cancer Centre, Department of Medicine and Pathology, University of Saskatchewan, Canada. E-mail: j.sutcliffe@usask.ca

- **Amsterdam criteria**

  - Higher risk for colorectal cancer (−70% for men and −30% for females), endometrial cancer (−70%) and also for ovarian, upper urinary tract, stomach and breast cancer [12].
  - Higher incidence of extracolonic cancers, when compared with HNPCC families [13].
  - Later age at onset of cancers, e.g. for colorectal cancer the mean age at diagnosis is −56 years, for endometrial cancer −54 years and for ovarian cancer −49 years [12, 13].
  - Frequent left-sided localization of colorectal cancer [9].

  - The prevalence of hMSH6 constitutional mutations in families that fulfill the Amsterdam criteria is about 5-10% [9, 9].
Primary adnexal carcinoma vs cutaneous metastases

**Recommended panel**

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>Primary adnexal carcinoma, %</th>
<th>Cutaneous metastasis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK15</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>EC10</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>CK20</td>
<td>91-100</td>
<td>9-22</td>
</tr>
<tr>
<td>CEA</td>
<td>44-95</td>
<td>9-4</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td>14-64</td>
<td>18-28</td>
</tr>
<tr>
<td>NSE</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>CD15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### Primary adnexal carcinoma vs cutaneous metastases

**Recommended panel**

<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
<th>Primary adnexal carcinoma, %</th>
<th>Cutaneous metastases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>P40</td>
<td>69.100</td>
<td>0.22</td>
</tr>
<tr>
<td>CK13</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>EGC-40</td>
<td>44.45</td>
<td>8.4</td>
</tr>
<tr>
<td>CK20</td>
<td>91.100</td>
<td>23.56</td>
</tr>
<tr>
<td>CK19</td>
<td>14.64</td>
<td>16.28</td>
</tr>
<tr>
<td>Nkx2.1</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>CD15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Part III

### Controversies

Apocrine?  
Eccrine

![Image of histological classification](attachment:image.png)  
![Image of eccrine and apocrine sweat glands](attachment:image.png)
Apocrine vs. eccrine
? Role for EM

Benign adnexal tumors

Malignant adnexal tumors

Expression of Stem-Cell Markers (Cytokeratin 15 and Nestin) in Primary Adnexal Neoplasms—Clues to Etiopathogenesis
The end!