Primer of Immunohistochemistry (Epithelial Markers)

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bcl-2 Protein

- Functions in the governance of apoptosis, together with products of bax, p53, and other genes
- Expressed by basal cell carcinoma (*Br J Dermatol* 1993; 131: 28) but not by squamous cell carcinoma

BER-EP4

- Monoclonal antibody directed against a cell surface glycoprotein found on most but not all epithelial cells
- Expressed by basal cell carcinoma (*Am J Dermatopathol* 1993; 15: 45) but not by squamous cell carcinoma
Metatypical BCC
IMMUNOHISTOLOGIC DDX OF BCC AND ADNEXAL CARCINOMAS OF THE SKIN

- **Epithelial Membrane Antigen**
  - Cell membranous glycoprotein that is observed in the majority of human epithelial cells
  - Expressed in a diffuse fashion by truly glandular or sebaceous neoplasms; if present at all in BCC, EMA is restricted to areas of divergent differentiation

- **Carcinoembryonic Antigen**
  - Cell surface glycoprotein that is produced by a wide variety of glandular and other epithelial cells, including normal sweat glands and sudoriferous neoplasms
  - Expressed in adenoid cystic carcinoma of the skin and other forms of adnexal neoplasia that may be confused with adenoid basal cell carcinoma, whereas all BCC variants except “eccrine epithelioma” are non-reactive for this marker
EMA– Adenoid BCC

CEA+ Adenoid Cystic CA of Skin
- **Epithelial Membrane Antigen**
  - Expressed by approximately 75% of desmoplastic trichoepitheliomas, but not by any BCC variant except for possibly focal reactivity in “eccrine epitheliomas”

- **Chromogranin**
  - Expressed in most DTEs but not most BCCs
DTE-- Positive EMA

DTE-- Positive Chromogranin
One report (Smoller BR, et al.: Br J Dermatol 1993; 131:28) found immunostains for bcl-2 protein to be useful in separating BCC from classic trichoepithelioma.

(Fitzpatrick M, et al.: Am J Clin Pathol 1995; 103: 508) has not borne out that contention; at present, morphology alone must be used to make the distinction between BCC and “usual” trichoepithelioma.
“Trichoepithelioma”
bcl-2 in BCC
## TRICHOEPITHELIOMA (N=53)

<table>
<thead>
<tr>
<th></th>
<th>Bcl-2</th>
<th>CD34</th>
<th>BER-EP4</th>
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<tbody>
<tr>
<td>USABLE STAINS</td>
<td>43</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>36</td>
<td>1 (desmoplastic)</td>
<td>30</td>
</tr>
<tr>
<td>NEGATIVE</td>
<td>7</td>
<td>41</td>
<td>17</td>
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<tr>
<td>COMMENTS</td>
<td>9 with peripheral accentuation pattern</td>
<td>15 with stroma surrounding tumor focally positive</td>
<td>--</td>
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</tbody>
</table>
• **Keratin & Epithelial Membrane Antigen**
  
  • Reproducibly expressed multifocally in sarcomatoid carcinomas of the skin, but not in true cutaneous mesenchymal malignancies
Sarcomatoid Carcinoma of Skin
### TUMOR KER EMA S100 VIM

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>KER</th>
<th>EMA</th>
<th>S100</th>
<th>VIM</th>
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<tbody>
<tr>
<td>SCC</td>
<td>+</td>
<td>+/-</td>
<td>0</td>
<td>+/-</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
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<tr>
<td>AFX &amp; OTHER</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>SARCOMAS</td>
<td></td>
<td></td>
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**DDX OF SARCOMATOID BCC & SCC OF THE SKIN**

Monday, April 2, 12
Keratin Positivity in Sarcomatoid Carcinoma of Skin
Angiosarcoma–like Squamous Cell Carcinoma of Skin
Cytokeratin + Pseudovascular Squamous Carcinoma of Skin
Epithelioid (Carcinoma-like) Angiosarcoma
• Potential positivity for *keratin*
• Reactivity with *B72.3*
Some reported cases of keratin+ EASDST represent simple technical artifacts due to faulty antibody titering; **H O W E V E R,**

• Other examples have had confirmation of keratin content by Western blot and/or mRNA hybridization.....

• The latter probably reflects “atavistic” activation of the keratin gene complex in EASDST, which, among all soft tissue tumors, exhibits this aberrant trait most often for reasons that are currently unknown
HOW TO AVOID MISDIAGNOSIS OF EAS BECAUSE OF ABERRANT KERATIN REACTIVITY

- PANEL APPROACH!!!
  Epithelial membrane antigen -
  \textit{Ulex europaeus} I+
  CD31+
  CD34+
  von Willebrand factor +/-
Epithelioid Angiosarcoma of the Skin

CD31 Positivity

CD34 Positivity

Epithelioid Angiosarcoma of the Skin
DDX OF ADENOID SCC AND SWEAT GLAND

- **CARCINOEMBRYONIC ANTIGEN**
  - Present in roughly 75% of sweat gland carcinoma variants but not in primary cutaneous SCC

- **S100 PROTEIN**
  - Observed in approximately 60% of sudoriferous malignancies but not in SCC of the skin

  \textit{CONJOINT EFFICACY OF CEA+S100---- 80-85%}

- **B72.3**
  - Discriminating power between SCC and SGC is still being studied
Adenoid (Pseudoglandular) Squamous Cell Carcinoma

Sweat Gland Carcinoma with Squamous Metaplasia
B72.3+ Sweat Gland Carcinoma
MALIGNANT CLEAR CELL TUMORS OF THE SKIN: Differential Diagnosis

Clear cell (hydropic) BCC & SCC
Clear cell eccrine adenocarcinoma
Sebaceous carcinoma
Tricholemmal carcinoma
Metastatic clear cell adenocarcinoma of viscera
Clear (balloon) cell malignant melanoma
Clear Cell Basal Cell Carcinoma
CLEAR CELL BASAL CELL CARCINOMA: *Immunophenotype*

- Pan-Keratin +
- BER-EP4 +
- AE13/AE14 (-)
- EMA (-)
- CEA (-)
Clear Cell Squamous Cell Carcinoma
CLEAR CELL SQUAMOUS CELL CARCINOMA: Immunophenotype

- Pan-Keratin +
- BER-EP4 (-)
- AE13/AE14 (-)
- EMA (+/-)
- CEA (-)
- S100 protein (-)
Clear Cell Eccrine Carcinoma
CLEAR CELL ECCrine CARCINOMA: Immunophenotype

- Pan-Keratin +
- BER-EP4 (+/-)
- AE13/AE14 (-)
- EMA (+)
- CEA (+/-)
- S100 protein (+/-)
CEA+ Clear Cell Eccrine Carcinoma
Sebaceous Carcinoma
SEBACEOUS CARCINOMA: Immunophenotype

- Pan-Keratin +
- BER-EP4 (+/-)
- AE13/AE14 (-)
- EMA (+ with multivacuolar cytoplasmic pattern)
- CEA (-)
- S100 protein (-)
Trichilemmal Carcinoma
TRICHILEMMAL CARCINOMA: 
*Immunophenotype*

- Pan-Keratin +
- BER-EP4 (-)
- AE13/AE14 +
- EMA (+/-)
- CEA (-)
- S100 protein (-)
Metastatic Renal Cell Carcinoma
Metastatic Clear-Cell Carcinoma of Ovary
METASTATIC CLEAR CELL ADENOCARCINOMA: *Immunophenotype*

- Pan-Keratin +
- BER-EP4 (+/-)
- AE13/AE14 (-)
- EMA +
- CEA (+/-)
- S100 protein (+/-)
- [CA-125 or PLAP may be +]
CA-125+ Metastatic Clear Cell Ovarian Carcinoma
Balloon Cell Melanoma
CLEAR (BALLOON) CELL MELANOMA: *Immunophenotype*

- Pan-Keratin (-)
- BER-EP4 (-)
- AE13/AE14 (-)
- EMA (-)
- CEA (-)
- S100 protein +