Salivary Gland Pathology in the Molecular Era
Old Friends, Old Foes, & New Acquaintances

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Agenda

- Old Friends
- Old Foes
- Shifty Acquaintances

Old Friends

Mucoepidermoid Carcinoma

- Incidence
  - Most common malignant salivary gland tumor (children and adults)
  - Major and minor salivary glands
  - Peak incidence 5th to 6th decades
- Clinical
  - Mass lesion
  - Surgical treatment with margins
Histology

- Mucus cells and cysts
- Epidermoid cells
- Intermediate cells
Salivary Gland Tumors

<table>
<thead>
<tr>
<th>Tumor specific</th>
<th>General grading</th>
<th>Grading by Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoepidermoid</td>
<td>Epithelial-myoepithelial</td>
<td>Salivary Duct carcinoma</td>
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<tr>
<td>Adenoid cystic carcinoma</td>
<td>Adenocarcinoma, NOS</td>
<td>Polymorphous low-grade</td>
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No Grading

Acinic cell carcinoma

Mucoepidermoid Translocation

- t(11;19)(q21;p13)
- MECT1-MAML2
  - MECT1: also known as CRTC1, TORC1, WAM1P1
    - cAMP response element binding protein (CREB) regulated transcriptional coactivator
  - MAML2: Notch coactivator
  - Translocation activates Notch target genes independent of Notch ligands

MECT-MAML2 Translocation

Courtesy of Dr. Sanja Dacic
University of Pittsburgh
Variation MEC

- Oncocytic MEC
- Clear cell MEC
- Sclerosing MEC
- Psammomatous MEC
- “Warthin-like variant”?

Oncocytic MEC

<table>
<thead>
<tr>
<th>Site</th>
<th>Our Series</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>8/11 Parotid (73%)</td>
<td>12/17 Parotid (71%)</td>
</tr>
<tr>
<td>Gender</td>
<td>5 Male</td>
<td>10 Male</td>
</tr>
<tr>
<td></td>
<td>6 Female</td>
<td>6 Female</td>
</tr>
<tr>
<td>Mean Age</td>
<td>58 years</td>
<td>59 years</td>
</tr>
</tbody>
</table>

Weinreb I, AJSP 33:409, 2009
Oncocytic MEC

- **Histology**
  - Predominant epithelioid oncycytic cells
  - Focal mucoepidermoid carcinoma areas or prominent mucinous differentiation

- **IHC**
  - p63 positive in the oncycytic cells
  - Mucin and PASD positive in mucus cells
Oncocytic Mucoepidermoid Carcinoma, p63

Oncocytic MEC

- Molecular
  - 10/14 (71%) positive for MECT1-MAML2 translocation


Clear cell Mucoepidermoid Carcinoma
Differential Diagnosis

- Clear cell (hyalinizing) carcinoma
Clear Cell Carcinoma

- Incidence
  - Rare
  - <1% of salivary gland tumors

- Clinical
  - Minor >> major
  - 21% in parotid
  - Peak in 6th to 8th decades

Clear Cell Carcinoma

- Cytology
  - Clear cells
  - Glycogen content variable
  - Focal eosinophilia, rare squamous
  - Mucocytes usually absent

Clear Cell Carcinoma

- Other histologic features
  - Duct and gland lumens absent
  - Invasion
    - Perineural
    - Stromal
  - Stromal hyalinization
    - “Clear cell hyalinizing carcinoma”
Clear Cell Carcinoma

- Immunohistochemistry
  - CEA +
  - EMA +
  - Myoepithelial markers negative
  - p63 uniformly positive
  - CK5/6 uniformly positive
Clear Cell Carcinoma

- Treatment
  - Surgical resection with clear margins

- Prognosis
  - Excellent prognosis
  - Rarely metastasizes or causes death
  - Aggressive cases
    - Increased anaplasia
    - Increased mitotic activity

- t(12;22)
- EWSR1-ATF1 Translocation

  Similar to the translocation seen in clear cell sarcomas of tendons and aponeuroses, angiomatoid fibrous hystiocytoma, and clear-cell sarcomas of the gastrointestinal tract

Variant Morphology

- Oncocytic MEC
- Clear cell MEC
- Sclerosing MEC
- Psammomatous MEC
- "Warthin-like variant"?
Old Foes

Adenoid Cystic Carcinoma

- Incidence
  - Relatively common
  - Any salivary gland location
- Clinical
  - Mass lesion
  - Nerve palsies
  - Surgical treatment with margins
Adenoid Cystic Carcinoma

- Histology
  - Tubular, cribriform, solid patterns
  - Solid has worse behavior
  - Perineural invasion
  - Nuclei small, dark, and angulated

Adenoid cystic carcinoma, cribriform

Adenoid cystic carcinoma, tubular
Adenoid cystic carcinoma, solid

Adenoid Cystic Carcinoma, perineural invasion

- **IHC**
  - CKIT and bcl-2 positive
  - Epithelial cells: cytokeratins
  - Myoepithelial cells: p63, SMA, CK5/6
Adenoid Cystic Translocation

- t(6;9) (q22-23; p23-24)
- MYB-NFIB
  - MYB
    - Transcription factor with an important role in cell proliferation, apoptosis, and differentiation
    - Highly expressed in immature proliferating cells, and down-regulated as cells become more differentiated
    - Expressed in translocation in myoepithelial cells
  - NFIB: nuclear factor 1B

Translocation: FISH & IHC


High Grade Transformation

- Clinical
  - Tumor progression with aggressive disease
  - May have clinical history of adenoid cystic carcinoma
- Histology
  - Low grade areas and high grade areas
  - Epithelial predominance
  - Necrosis
  - Vascular invasion
Adenoid cystic carcinoma with high grade transformation

High Grade Transformation

- Immunohistochemistry
  - Loss of myoepithelial component
    - SMA, p63, calponin negative
    - All cells stain with cytokeratin
  - Strong p53 staining
  - High proliferative rate (Ki-67)
Epithelial-Myoepithelial Carcinoma

- Incidence: Rare
- Clinical: Mass lesion
  - 30% are encapsulated
  - Parotid 60%, palate 10%
- Histology
  - Epithelial: Tubules and ducts
  - Myoepithelial: Surrounds epithelial cells
  - Dense basement membrane material
Epithelial-Myoepithelial Carcinoma

- IHC
  - Epithelial markers
  - Myoepithelial markers
  - CKIT positive (70%)
  - Bcl-2 positive (70%)

Epithelial-Myoepithelial Carcinoma

- Prognosis
  - 95% disease specific prognosis
  - Poor prognostic markers
    - Necrosis
    - Angiolymphatic invasion
    - Positive surgical margins

Prognosis

- 95% disease specific prognosis
- Poor prognostic markers
  - Necrosis
  - Angiolymphatic invasion
  - Positive surgical margins
Polymorphous Low Grade

- Histology
  - Mixed growth patterns
  - Open nuclei, bland
  - Perineural and stromal invasion

Polymorphous Low Grade

- Incidence
  - Usually in oral cavity, palate
- Clinical
  - Mass lesion
  - Surgical treatment with margins

Polymorphous low grade adenocarcinoma
Polymorphous low grade adenocarcinoma

- Immunohistochemistry
  - GFAP negative
  - Bcl-2 positive
  - S100 positive
  - CKIT +/-
Acinic Cell Carcinoma

- Histology: variable
  - Serous
  - Papillary-cystic
  - Tubulolobular
- Special stains
  - Cytoplasmic zymogen granules
    - PAS, diastase resistant
  - DOG1 and carbonic anhydrase VI
Zymogen Poor Acinic Cell Carcinoma

• Major differential diagnoses
  • Acinic cell carcinoma
    • 12% on re-review were MASC
    • ~50% of zymogen poor were MASC
  • Adenocarcinoma, NOS
    • 38% on re-review were MASC
  • Mammary analog secretory carcinoma
  • Low grade cribriform cystadenocarcinoma

Chiosea S1, AJSP 36:343, 2012
Mammary Analogue Secretory Carcinoma

- **Clinical**
  - Rare tumor, but not well described yet
  - Mean age 45
  - Males > Females
  - 69% in major salivary glands
  - 22% with nodal metastasis
  - 92 month disease free survival


- **Histology**
  - Circumscribed, but not encapsulated
  - Lobulated mass divided by fibrous septae
  - Microcystic or tubular
  - Occasional unusual growth
    - Solid or macrocystic
  - Bubbly secretion in microcysts (PAS +)
Mammary Analogue Secretory Carcinoma

Immunohistochemistry
- Strong cytokeratin (7, 8, 18)
- Strong diffuse S100
- GCDFP (70%)
- Mammoglobin (100%)
Mammary Analogue Secretory Carcinoma

- *ETV6-NTRK3*
- t(12;15)

FISH image courtesy of Julia Bridge, MD

Major differential diagnoses
- Acinic cell carcinoma
- Adenocarcinoma, NOS
- Other ductal derived tumors
Agenda

- Old Friends
  - Mucoepidermoid Carcinoma
  - Variants of MEC
- Old Foes
  - Adenoid cystic carcinoma
  - Epithelial myoepithelial carcinoma
- Shifty Acquaintances
  - Acinic cell carcinoma
  - Mammary analog secretory carcinoma