Something Olde, Something New, Something Borrowed, Something Blue

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CHAPTER 7
Tumours of salivary glands
Malignant tumours
Borderline tumours
Benign tumours
Other epithelial lesions
Soft tissue lesions
Haematolymphoid tumours

General Considerations
- <1% of all tumors
- Most common in adults
- Fine needle aspiration first line screening test
- Little known about etiology
- Clinic stage is important
- Molecular techniques slow to catch on

Salivary Gland Genetics

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphic adenoma</td>
<td>PLAG1 (8q12) (70%)</td>
<td>Up to 90%</td>
</tr>
<tr>
<td></td>
<td>AMM2 (2q32-33) (30%)</td>
<td></td>
</tr>
<tr>
<td>Basal cell adenoma</td>
<td>CTNNB1 mutation</td>
<td>70-80%</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>CTNNB1-MAK62 (19q13.3-13.4)</td>
<td>80%</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>(14q12.1-q13) + 5-7q21-q23 trans</td>
<td>80% and 10%</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>MAFB-MNK1 or MKK3-MNK1</td>
<td>60-70%</td>
</tr>
<tr>
<td>Polymorphous adenocarcinoma</td>
<td>ARID1-PRKD1 (PRKD1, PRKD2) or PRKD1 hotspot</td>
<td>20-50%</td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>TP53, HRAS, KEAP1, PTEN mutations;</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>NRAS amplification</td>
<td></td>
</tr>
<tr>
<td>Secretory carcinoma</td>
<td>ETV6-NTRK3 (RET, MET)</td>
<td>&gt;95%</td>
</tr>
<tr>
<td></td>
<td>KIT (KITL)</td>
<td></td>
</tr>
<tr>
<td>Intraductal carcinoma</td>
<td>HRAS, RET or RET-TRIM27</td>
<td>50%</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>EWSR1-ATF1 (CREM)</td>
<td>90%</td>
</tr>
</tbody>
</table>

Salivary Glands
2005 edition: 42 diagnoses
2017 edition: 45 diagnoses
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Benign versus Malignant

- Rate of growth
- Relationship with surrounding structures
- Circumscription
- Cytological atypia

As a general rule:
The smaller the involved salivary gland . . .
The higher the possibility of the tumor being malignant

Case
- 74 y.o.
- Female
- Enlarged right parotid gland
- FNA was performed on a 4.0 cm mass
- Lobectomy was performed
**Acinic Cell Carcinoma**

**Malignant epithelial salivary gland neoplasm demonstrating serous acinar cell differentiation with cytoplasmic zymogen secretory granules**

- **Incidence**
  - ~ 6% of salivary gland tumors (2nd to MEC)
  - ~ 10-12% of all malignant salivary gland tumors
- **Sex**: Female > Male (3:2)
- **Age**: Wide range
  - Mean: 5th decade
  - 2nd most common malignant salivary gland tumor in children (after MEC)
- **Presentation**: Slowly growing mass
  - Vague pain – usually for years!

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<table>
<thead>
<tr>
<th>Site</th>
<th>Parotid gland most common (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parotid is largest salivary gland, comprised nearly exclusively of serous type acini</td>
</tr>
<tr>
<td></td>
<td>Minor salivary glands 2nd most common site (but doubt: may be SC, PAC-C)</td>
</tr>
<tr>
<td></td>
<td>Intraoral, buccal mucosa, upper lip, and palate specifically (5%)</td>
</tr>
<tr>
<td></td>
<td>Most common bilateral salivary gland malignancy</td>
</tr>
<tr>
<td></td>
<td>Dwarfed by bilateral Warthin tumor and pleomorphic adenoma</td>
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</tbody>
</table>

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**Acinic cell carcinoma**

- **Site**
  - Parotid gland most common (95%)
  - Parotid is largest salivary gland, comprised nearly exclusively of serous type acini
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  - Intraoral, buccal mucosa, upper lip, and palate specifically (5%)
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  - Parotid is largest salivary gland, comprised nearly exclusively of serous type acini
  - Minor salivary glands 2nd most common site (but doubt: may be SC, PAC-C)
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Acinic cell carcinoma

Cell types

- **Serous acinar cells**: Large, polygonal cells with abundant lightly basophilic, granular cytoplasm
  - Strong resemblance to normal serous acini cells
  - Dense, gray to blue to purple, fine to coarse zymogen granules
- **Intercalated duct type cells**: Surround luminal spaces and tend to be smaller, eosinophilic to amphophilic cells with central nuclei
- **Nonspecific glandular cells**: Round to polygonal, often syncytiial, and smaller than acinar cells
  - Amphophilic to eosinophilic cytoplasm without granules
- **Clear cells**: Have nonstaining cytoplasm with prominent cell borders (no glycogen)
- **Vacuolated cells**: Have clear, large cytoplasmic vacuoles
  - PAS and mucicarmine negative

Histologic Findings

- Lymphoid infiltrate, often with prominent germinal centers, may be seen
  - “Tumor-associated lymphoid proliferation” (TALP)
  - May simulate a lymph node (not metastasis)
  - CAM5.2 is + in interfollicular dendritic cells in lymph node
- Stromal fibrosis/desmoplasia is uncommon
Acinic cell carcinoma
Special Studies

- PAS(+), diastase-resistant zymogen granules
  - Reaction can be patchy and limited
- Immunohistochemistry is nonspecific and unpredictable
  - Positive: DOG1, SOX10, NR4A3
  - Negative: S100 protein, mammaglobin
- NR4A3 recurrent rearrangement (84%)
  - t(4;9)(q13;q31)
- HTN3-MSANTD3 fusion defines a small subset

Management and Prognosis

- Complete surgical excision
  - Incomplete excision portends poor prognosis
- Radiation only for incompletely excised tumors or advanced stage disease
- Generally, good prognosis
  - 5-year 80 – 90% (disease specific)
  - 10-year 65%
- Clinical stage more reliable than histologic grade or growth pattern in determining outcome
- Recurrences in ~35% of cases (within 5 years)
High Grade Transformation

- High-grade transformation (dedifferentiation) into high-grade carcinoma (including small cell carcinoma) heralds poor prognosis
- Up to 15% of acinic cell carcinoma undergo high grade transformation
- Parotid gland only
- Age: Mean: 64 years ~ 20 years older than conventional
- Sex: Female > Male (3:2)

High Grade Transformation

- Conventional low grade tumor is juxtaposed and/or blended with areas of high grade tumor
- Undifferentiated (small or large cell) carcinoma or poorly differentiated adenocarcinoma
  - Small or large cell neuroendocrine type
- Increased mitoses, including atypical forms
- Vascular and perineural invasion
- Central comedo-type of necrosis
- Anaplastic cells with large vesicular pleomorphic nuclei, prominent nucleoli and abundant cytoplasm

Case

- 57 y.o.
- Female
- Presented with an enlarged parotid gland
- FNA was performed
- Superficial parotidectomy was performed

Secretory Carcinoma

- Where did the tumor come from (2010, described by Skálová, et al.)?
  - Acinic cell carcinoma
    - 12% on re-review were SC
  - Adenocarcinoma, NOS
    - 38% on re-review were SC
  - Other ductal derived tumors
    - Mucoepidermoid carcinoma, cystadenocarcinoma
Secretory Carcinoma

**Secretory carcinoma is a generally low-grade salivary carcinoma characterized by morphologic resemblance to its mammary counterpart with an ETV6 associated gene fusion**

- **Sites:**
  - Salivary gland
  - Breast
  - Thyroid gland
  - Skin
  - Genitourinary tract

**Age:** Middle aged
- Mean: 47 years
- Range: 7 – 88 years

**Sex:** Male > Female (1.3:1)

**Site:** Major salivary glands and oral cavity (88%) > > upper lip, retromolar trigone

Lobulated, pushing growth (no capsule generally)
- Invasive growth into parenchyma (40%)
  - Perineural invasion (20%)
- Microcystic to glandular appearance (45%)
- Papillary (30%); Solid or macrofollicular (20%)
- Oligocystic (<5%)
- Eosinophilic, homogenous or bubbly secretory (colloid-like) material in the lumen
Secretory Carcinoma
Histologic Features

- Vesicular nuclei with finely granular chromatin but distinct centrally placed nucleoli
- Ample pale pink, granular or vacuolated cytoplasm
- Pleomorphism is limited
- Necrosis is absent
- Mitoses are rare

- When present → HGT
- When present → HGT
- >3/2 mm² → HGT
**Secretary Carcinoma Immunohistochemistry**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Reactivity</th>
<th>Pattern</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammaglobin</td>
<td>Positive</td>
<td>Cell membrane &amp; cytoplasm</td>
<td>Strong, diffuse</td>
</tr>
<tr>
<td>S100 protein</td>
<td>Positive</td>
<td>Nuclear &amp; cytoplasmic</td>
<td>Strong, diffuse</td>
</tr>
<tr>
<td>GCFFP-15</td>
<td>Positive</td>
<td>Nuclear</td>
<td>Strong, diffuse</td>
</tr>
<tr>
<td>STAT5</td>
<td>Positive</td>
<td>Nuclear</td>
<td>Strong, diffuse</td>
</tr>
<tr>
<td>GATA3</td>
<td>Positive</td>
<td>Nuclear</td>
<td>Strong, diffuse in most tumor cells</td>
</tr>
<tr>
<td>CK7</td>
<td>Positive</td>
<td>Cytoplasmic</td>
<td>Strong, diffuse</td>
</tr>
<tr>
<td>CK-pan</td>
<td>Positive</td>
<td>Cytoplasmic</td>
<td>Strong, diffuse</td>
</tr>
<tr>
<td>Adipophilin</td>
<td>Positive</td>
<td>Cytoplasmic</td>
<td>Large lipid droplets</td>
</tr>
<tr>
<td>p63</td>
<td>Negative</td>
<td></td>
<td>+ in Acinic cell carcinoma</td>
</tr>
<tr>
<td>DOG1</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Images:**
- Mammaglobin
- S100 protein
- p63

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Secretory Carcinoma: Molecular Findings

- **Definitional** specific recurrent balanced chromosomal translocation ETV6-NTRK3 fusion transcript at t(12;15)(p13;q25)
  - Chimeric tyrosine kinase identical to secretory breast carcinoma (triple negative, basal phenotype), mesoblastic nephroma and infantile fibrosarcoma
- Rarely, ETV6-RET, ETV6-MET, ETV6-MAML3, VIM-RET, MYB-SMR3B may be detected
- Before targeted therapy (Larotrectnib, Entrectinib, Selpercatinib, Pralsetinib), must do NGS to confirm specific findings (**TRK** vs. **RET**)

Secretory carcinoma
Prognosis and Predictive Behavior

- Lymph node metastases in about 25%
- Local recurrence is about 20%
- Distant metastases in about 2%
- High grade transformation:
  - 5%; Male; 56 years; Solid, necrosis, >3/2 mm²
- Disease free survival: 7.5 years
  - Only about 10% die with disease
- Clinical stage and high grade transformation are poor prognostic markers

Pleomorphic adenoma
Clinical

- The MOST common salivary gland neoplasm
  - So, consider it every time
- Age: 30 – 60 years
- Sex: Equal
- Site: Parotid most common site (superficial > deep)
  - Palate next most common
- Slow growing, painless, lobular mass
  - Can reach huge size
Pleomorphic Adenoma

**Macroscopic**

- Circumscribed
- Tumor may be multinodular
- Tumor has “pseudopods” that bulge outwards

**Histology**

- Tumor is epithelial (ductal), basal, and myoepithelial with mesenchymal component (myxoid, chondroid, hyaline, osseous)
- Remarkably variable histology (pleomorphic)
  - Solid, tubular, trabecular, cystic
  - Cells literally “melt” into the chondromyxoid background stroma
  - Stroma may be heavily fibrotic/hyalinized
  - Spindled, epithelioid, *glandular*, & plasmacytoid cells
  - Squamous metaplasia is common
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Salivary Duct Carcinoma (SDC)

**Definition**

- Aggressive malignant epithelial neoplasm histologically with apocrine appearance resembling high-grade apocrine breast carcinoma with strong, diffuse nuclear androgen receptor reactivity
- Approximately 10% of malignancies
- Age: Older, with peak in 7th decade
- Sex: Male > Female (2 — 4:1)
- Site: Parotid gland >>> other sites (rare in minor glands)
- Presentation: Recent rapid growth
  - Nerves: Facial nerve paresthesia, pain, paresis, paralysis

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Salivary Duct Carcinoma
Pleomorphic Adenoma Origin

- Hyalinized/sclerotic nodule may be all that remains of pleomorphic adenoma
- Molecular evidence of pleomorphic adenoma
  - PLAG1 (33%) or HMG2 (13%)
  - 15—60% will show molecular support without obvious histology support
- Activating mutations and amplifications of oncogenes: PIK3CA, HRAS, ERBB2, BRAF
- Inactivating mutations or deletions of tumor suppressors: TP53, CDKN2A, PTEN, ATM
- ERBB2 (Her-2) amplification only in SDC ex PA (rare)

Salivary Duct Carcinoma (SDC)
Microscopic Features

- Unencapsulated, poorly circumscribed, widely infiltrative
- Cysts with comedonecrosis
- Marked, dense, desmoplastic (hyalinized) fibrosis
- Concurrent/preexisting pleomorphic adenoma in ~80%
- Cells are arranged in papillary-cribriform to band-like solid patterns
  - “Roman bridge” architecture is classic
- Moderate to marked pleomorphism of apocrine cells
  - Large, prominent nucleoli and hyperchromatic chromatin
- High mitotic index

Invasive (>1.5 mm)
Salivary Duct Carcinoma (SDC) Immunohistochemistry

- **Positive:**
  - Epithelial markers (including CK7)
  - Androgen receptor
  - HER-2/neu (40-50%)
  - GCDFP15
  - p53
  - EGFR
- **Negative:**
  - p63
  - CK5/6
  - GFAP

Androgen Receptor
Salivary Duct Carcinoma (SDC)

Treatment and Outcome
- Aggressive multimodality therapy required
- Surgery (including lymph node dissection)
- Radiation
- Androgen deprivation therapy and chemotherapy
- Poor prognosis overall (< 35% 5-year survival)
  - Local recurrences in up to 50% (usually <5 years), often multiple
  - Lymph node metastases (up to 25%)
  - Distant metastases (up to 70%)
    - Lung, bone, liver, brain, skin

Prognosis
- Prognostically significant factors (in order)
  - Grade (high grade usually die from disease)
  - Stage (T2 or higher)
  - Extent of invasion (>1.5 mm poor prognosis)
  - Proportion of tumor that is carcinoma (>50%)
  - Large tumor size (>4 cm)
  - Proliferation index (Ki-67) (>50%)
  - Histologic subtype (undifferentiated is worst)
  - Margin status (positive increases recurrence)

Differential Diagnosis
- Intraductal carcinoma (replaces low grade cribriform cystadenocarcinoma/low grade salivary duct carcinoma):
  - Predominantly papillary, cystic tumor, with low-grade cytologic features, absent comedonecrosis and lacks infiltration
- Carcinomas with High Grade transformation
  - Oncocytic carcinoma (no apocrine; more granular cytoplasm), epithelial-myoepithelial carcinoma, myoepithelial carcinoma
- Mucoepidermoid Carcinoma, High Grade
  - Lacks prominent papillary or cribriform patterns, shows goblet cells, epidermoid and transitional cells
  - Positive: p63, CK5/6, p40; Negative: AR
- Metastatic Squamous cell Carcinoma
  - Prominent lymphoid reaction, squamous differentiation, keratinization, may have necrosis
  - Positive: p63, CK5/6, p40; Negative: AR

Mucoepidermoid Carcinoma

Clinical
- A malignant epithelial neoplasm with variable components of mucous, epidermoid, and intermediate cells, with columnar, clear cell and oncocytic populations
- Most common malignant salivary gland tumor
- Age: Wide range
- Sex: Female > Male (3:2)
- Site: Major (parotid): 45% Minor: 48%
- Presentation: Painless, firm, fixed, slow-growing mass

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**Macroscopic Features**
- Circumscribed, partially encapsulated, or poorly defined periphery
- Cut surface
  - Cystic, sometimes with blood
- Highly variable size
  - < 1 cm to large disfiguring masses

**Histologic Features**
- Cystic spaces
  - Often filled with mucin, sometimes with papillary projections
- Dissecting fibrosis;
- Tumor Associated Lymphoid Proliferation (TALP)
- Perineural and vascular invasion may be seen
- Neoplasm consists of:
  - Epidermoid cells: nests polygonal cells, focal keratinization
  - Intermediate cells: large polygonal to small basal cells
  - Mucus cells: Intracytoplasmic mucin (goblet-cell): vacuolated or clear cytoplasm
- Necrosis, anaplasia, and mitoses variably present
- Spilled mucus: Incites inflammatory response
Mucoepidermoid Carcinoma Grading

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracystic component &lt; 20%</td>
<td>2</td>
</tr>
<tr>
<td>Neural invasion present</td>
<td>2</td>
</tr>
<tr>
<td>Necrosis present</td>
<td>3</td>
</tr>
<tr>
<td>4 or more mitoses per 10 HPF</td>
<td>3</td>
</tr>
<tr>
<td>Anaplasia</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total point score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>0-4</td>
</tr>
<tr>
<td>Intermediate grade</td>
<td>5-6</td>
</tr>
<tr>
<td>High grade</td>
<td>7 or more</td>
</tr>
</tbody>
</table>

Carcinomas of the Major Salivary Glands
Histopathology Reporting Guide

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### Take Home Points

- Benign tumors are much more common than malignant
- Major salivary glands affected more often than minor
- Significant morphologic overlap between categories
- Pleomorphism, increased mitoses and tumor necrosis increase grade and risk of recurrence in most tumors
- FNA is a screening tool to guide but not dictate management
- Molecular findings can assist in some cases