Salivary Gland Neoplasms

R. Michelle Cox, MD
University of Arkansas for Medical Sciences
Objectives

• Accurately diagnose some less common neoplasms identified within the salivary glands
• Compare and contrast these neoplasms with other entities in the differential diagnoses
• Know the pertinent immunohistochemical and molecular findings of these neoplasms
Case #1

• A 47-year-old male presents with a right-sided parotid gland mass that he states has been present for approximately 18 months. On gross examination of the parotidectomy, a 2.7 cm tan, firm well-circumscribed mass with a possible thin capsule is identified.
Case #1

- **Immunohistochemical Profile:**
  - Pan-cytokeratin: Patchy Positive
  - CK 5/6: Patchy Positive
  - P63: Diffuse Positive
  - SMA: Negative
  - S-100: Patchy Positive
  - Calponin: Patchy Positive
Case # 1

• Diagnosis
  – Myoepithelioma
Myoepithelioma

• Composed exclusively of myoepithelial cells
  – Some allow < 5% ductal component

• Account for approximately 1-2% of salivary gland neoplasms

• Most common sites in salivary tissue:
  – Parotid gland: 40-50%
  – Minor salivary glands: 20-25%
  – Submandibular gland: 10-15%
Myoepithelioma

- Most common in patients 40-50 years old, but broad age range (9-95 years)
- About equal involvement in male:female
- Most common presentation is as a slowly growing mass present for months to years
Myoepithelioma

• Gross examination shows a well-circumscribed, 1-5 cm (usually are < 3 cm) mass varying from grey-white to tan in color
  – May have an ulcerated overlying mucosa in the palate

• Commonly appear encapsulated in the parotid gland, less commonly in the minor salivary glands
Myoepithelioma

• Behave similarly to pleomorphic adenomas, but are less likely to recur than pleomorphic adenoma
• Tumors with positive surgical margins are more likely to recur
Myoepithelioma

- Like PA, myoepitheliomas can rarely transform into a malignant tumor
  - Usually the tumors are long-standing or have recurred multiple times
Myoepithelioma

• Lesions have wide variation in architectural and cytologic patterns

• Architectural Patterns:
  – Solid
  – Microcystic
  – Trabecular
  – Reticulated
  – Mixture of architectural patterns is common
Myoepithelioma

• Cytologic Features
  – Spindle – most common
  – Plasmacytoid – more common in palate
  – Epithelioid
  – Clear cell
  – Oncocytic
  – Mixture of cell types may be present
Myoepithelioma

• Background stroma is present in varying amounts and can be myxoid or sclerotic with resultant variation from hypercellular lesions to hypocellular lesions with abundant intervening stroma
  – No chondroid component should be present
• Spindle cell myoepitheliomas tend to be hypercellular lesions with sparse stromal component
  – Some cases have a dense collagenous stromal component and can mimic SFT
• Most commonly have a fascicular architecture
• Central round to oval nuclei with eosinophilic cytoplasm
Myoepithelioma

• Plasmacytoid (hyaline cells) often appear as sheets and nests of cells with associated myxoid stroma

• Cells mimic plasma cells with eccentric nuclei and abundant eosinophilic cytoplasm
  – No perinuclear hof is present
• Epithelioid myoepitheliomas appear polygonal in shape with abundant eosinophilic cytoplasm and central nuclei
• Cells are arranged in solid sheets, trabeculae, or reticular patterns
Myoepithelioma

- Clear cells are polygonal in shape with abundant clear cytoplasm
- PAS positive – cytoplasm is filled with glycogen
- Cells are often arranged in sheets and nests with little intervening stroma
- Myoepitheliomas with predominant clear cell component are uncommon
Myoepithelioma

• Oncocytic cells have abundant granular eosinophilic cytoplasm and can appear spindled or more epithelioid

• Admixed focal populations of cells with clearing of the cytoplasm is often present, and cells with vacuolated cytoplasm reminiscent of sebaceous differentiation may be present

• Hyperchromatic, pleomorphic nuclei may be present

• Cells co-express CK and myoepithelial markers
Myoepithelioma

• Cells appear bland, with minimal to mild pleomorphism

• Focal areas of degenerative atypia with smudged appearing enlarged, hyperchromatic cells may be present

• Mitotic figures are not readily identified (up to 6 mitoses/ 10 high powered fields)
Myoepithelioma
Immunohistochemical stains

- Positive staining for pan-CK along with myoepithelial markers
  - CK 5/6
  - S-100
  - Calponin
  - P63
  - SMA

Oncocytic myoepithelioma – CK 5/6

Oncocytic myoepithelioma – S-100
Differential Diagnosis

• Myoepithelial Carcinoma
  – Infiltrative – most useful
  – Mitoses
    • Myoepitheliomas should not have atypical mitoses
  – Necrosis
  – Cellular atypia
    • Myoepitheliomas may have focal degenerative atypia
Differential Diagnosis

• Pleomorphic adenoma
  – Presence of ductal structures
  – Presence of characteristic myxochondroid mesenchymal matrix

• Plasmacytoma
  – May enter the differential dx in plasmacytoid predominant tumors
  – No perinuclear hof
  – Positive staining for CK and myoepithelial markers
Differential Diagnosis

• Spindle cell variant
  – Smooth muscle neoplasms
    • Myoepitheliomas have positive staining for both CK and S-100
    • Myoepitheliomas are encapsulated and well-circumscribed
  – Nerve sheath tumors
    • While both stain positive for S-100, myoepitheliomas have positive staining for CK
Differential Diagnosis

• Clear cell variant
  – Other predominantly clear cell neoplasms
    • Epithelial-myoepithelial carcinoma
      – Biphasic neoplasms with a ductal component present in IHC staining

• Clear cell hyalinizing carcinoma
  – Negative for myoepithelial markers

• Clear cell variant of mucoepidermoid carcinoma
  – Mucicarmine stain highlights intracellular mucin

• Clear cell variant of oncocytoma
  – Myoepithelial markers are negative

• Metastatic clear cell RCC
  – Negative for myoepithelial markers, positive for PAX 8
Case #2

• A 56-year-old female presents with a left parotid mass that has been present for approximately 12 months.
Immunohistochemical profile

- P63, SMA, calponin, and CK 5/6 is positive within the abluminal layer of cells

- CAM 5.2 is positive in both cell layers, but shows stronger staining within the luminal cells
Case #2

• Diagnosis:
  – Epithelial-myoepithelial carcinoma
Epithelial-Myoepithelial Carcinoma

• Accounts for about 1-2% of salivary gland tumors
• Most common in the 6\textsuperscript{th} to 7\textsuperscript{th} decade, but with a broad age range
• Slight female predominance is present
Epithelial-Myoepithelial Carcinoma

• Most common in the parotid gland (75%), with submandibular and minor salivary glands accounting for the majority of the remaining cases

• Presentation is usually as a slowly growing painless mass that has been present from a few months to many years and is about 2.5 cm in size (range 2-12 cm)
Epithelial-Myoepithelial Carcinoma

- On gross examination, it is a well-circumscribed, firm tan-white nodular or multi-nodular mass, may have areas with a cystic appearance
  - Minor salivary gland tumors may have more ill-defined borders
Epithelial-Myoepithelial Carcinoma

• Is a low-grade malignancy, with 5 year survival > 90%
• Has a tendency to recur locally
  – Local recurrence is seen in 1/3 to ½ of cases
  – A prolonged delay until recurrence can be seen (may be 10 years or more after initial presentation)
  – Increased risk of recurrence is seen with:
    • Positive surgical margins
    • Angiolympathic invasion
    • Necrosis
• Distant metastasis is uncommon, occurring in about 2% of cases
Epithelial-Myoepithelial Carcinoma

• Biphasic tumor with ductal epithelial cells and myoepithelial cells

• Invasion usually occurs in broad, pushing borders

• Overall has a nodular or multinodular architecture, with tubules and solid areas
  – Ductal epithelial cells are a single layer of cuboidal to columnar cells with eosinophilic cytoplasm forming the luminal layer in tubules
  – Myoepithelial cells may have one or multiple layers of abluminal cells which are polygonal and/or spindled in appearance, often with clear cytoplasm
Epithelia-Myoepithelial Carcinoma

• While there is usually a 2-3:1 ratio of myoepithelial:ductal cells, either cell type can predominate
  – Myoepithelial cells can predominate to the extent that cytokeratin stains are required to highlight the compressed ductal epithelial cell layer
Epithelial-Myoepithelial Carcinoma

- Eosinophilic material may be present within the tubular lumens
  - Material is PAS positive, mucicarmine negative
- Thick basement membrane type material can be seen surrounding the tubules
- Some tumors may have focal areas with cystic or papillary architectures
- Intraluminal calcifications may be identified
Epithelial-Myoepithelial Carcinoma
Epithelial-Myoepithelial Carcinoma

- Foci of squamous or sebaceous differentiation may be present
- Pleomorphism is mild, but degenerative atypia may rarely be present
- Mitotic figures are sparse (1-2/10 hpf)
- Perineural and angiolympathic invasion may be identified
- Areas of necrosis may be present
Immunohistochemical Profile

IHC stains highlight the biphasic cell populations

- Ductal epithelial cells
  - EMA and cytokeratin positive

- Myoepithelial cells
  - Positive for SMA, calponin, P63, CK 5/6
  - Positive for pan-CK, but usually show weaker positive staining than the ductal epithelial cells

- S-100 shows variable staining patterns and can be positive in both populations
Variant Morphologies

• Oncocytic and apocrine are the most common variants of epithelial-myoepithelial carcinoma seen
• Identified as variant morphology if > 50% of total tumor
• Oncocytic variant tends to affect an older population, presenting on average a decade later
Oncocytic Variant

• Has the same bilayered morphology as non-variant epithelial-myoepithelial carcinoma, but may be more difficult to discern
• Tubules are generally of a larger caliber and bilayered papillae are common
• Intraluminal calcifications are commonly seen
• Almost all oncocytic variant EMC have areas of sebaceous differentiation
• PTAH and anti-mitochondrial antibody stains are positive
Apocrine Variant

• The ductal component has eosinophilic cytoplasm with luminal apical snouts and decapitation secretions
• The ductal component may form solid and/or cribriform areas
• The nuclei are enlarged and vesicular, with prominent nucleoli
Apocrine Variant

- Myoepithelial cells often have clear cytoplasm.
- Sebaceous differentiation is not present; papillary architecture, and intraluminal calcifications are not as common.
- IHC stains for androgen receptor, GCDFP-15, and HER-2/neu are often positive.
Apocrine Variant
EMC with High Grade Transformation

- Clinically, presentation is typically of a mass that has recently rapidly enlarged in size
- Patients are usually older and present with larger size tumors (average 6 cm)
- May arise from transformation of the ductal component or myoepithelial component
EMC with High Grade Transformation

• No distinct morphology of the high grade transformation areas has been identified
  – Appears as a high grade malignant neoplasm

• Adjacent areas show more typical epithelial myoepithelial carcinoma
Differential Diagnosis

• Pleomorphic adenoma
  – Infiltrative at the edges of the neoplasm
  – Lack of chondromyxoid mesenchymal component
  – Myoepithelial cells are usually not predominantly clear in PA

• Myoepithelioma / Myoepithelial Carcinoma
  – Ductal epithelial cells present, may need IHC to highlight their presence
Differential Diagnosis

• Clear cell neoplasms
  – Clear cell hyalinizing carcinoma
    • No myoepithelial component
  – Clear cell oncocytoma
    • No biphasic population of cells
  – Clear cell predominant mucoepidermoid carcinoma
    • Three cell populations – epidermoid, intermediate, and mucinous
Case #3

- Patient is a 43-year-old male with a right buccal mass present for an unknown amount of time.
Case #3

- Immunohistochemical stains
  - S-100 – positive
  - Mammoglobin – positive
  - P63 – negative
  - Calponin - negative
  - GATA-3 – positive
  - DOG-1 – negative
  - PAS – stains intraluminal secretions
  - Mucicarmine – stains intraluminal secretions
Case #3

• Diagnosis
  – Mammary Analogue Secretory Carcinoma
Mammary Analogue Secretory Carcinoma (MASC)

• Recently described (2010, Skalova et al.) neoplasm named for similarities to secretory carcinoma of the breast
• Average age affected is 46 (range 21-75) with a slight male predominance
• Common presentation is as a slow-growing mass present for many months to years
Mammary analogue Secretory Carcinoma

- Most common location is the parotid gland, also identified in the minor salivary glands and submandibular gland
  - More commonly present in minor salivary glands than acinic cell carcinoma
- Average size is about 2 cm (range 0.7 to 5.5 cm)
Mammary Analogue Secretory Carcinoma

- Tumors have a rubbery consistency and are tan to grey-white
- May have a cystic component on gross exam, with white to yellow cystic fluid
Mammary Analogue Secretory Carcinoma

- Tumors appear well-circumscribed with an overall lobular architecture divided by fibrous septae
  - No capsule is present
- Cells are arranged in tubular, solid, papillary, cystic, and cribriform architectures
- Eosinophilic, dense, colloid-like to bubbly-appearing secretions are present which are PAS and mucicarmine positive
Mammary Analogue Secretory Carcinoma

- Cytoplasm is abundant, light eosinophilic, and may appear vacuolated or granular
- Hobnailing of cells may be present
- Rare cells with intracytoplasmic mucin may be highlighted with mucicarmine staining
- PAS stains may show globular PAS-positive cytoplasmic inclusions, but no zymogen granules
Mammary Analogue Secretory Carcinoma

- Cells have low grade nuclear features with vesicular nuclei and central nucleoli
- Nuclei show mild pleomorphism and rare mitotic figures
- Perineural invasion can be present
- No angiolymphatic invasion has been described
- Necrosis is absent
Mammary Analogue Secretory Carcinoma

- Immunohistochemical findings
  - Positive for CK and EMA
  - Myoepithelial/basal markers are usually negative, but may see rare incomplete basal cell layers
  - Positive for S-100, mammaglobin, GATA3, GCDFP-15
  - Cytoplasm contains lipid and adipophilin shows positive staining
  - DOG-1 is negative
Mammary Analogue Secretory Carcinoma

• Molecular
  – Balanced chromosomal translocation: \( t(12;15) \) (p13;q25)
    • Fusion gene between ETV6, a transcription regulator, on chromosome 12 and NTRK3, a membrane receptor tyrosine kinase, on chromosome 15
  – Same translocation as identified in secretory carcinoma of the breast, infantile fibrosarcoma, and cellular mesoblastic nephroma
Mammary Analogue Secretory Carcinoma

- May show local recurrence, lymph node mets, and less commonly distant metastatic disease
- In original series of 16 cases, 2 patients died of disease
  - One developed distant metastases to the lung, pleura, and pericardium and one had multiple local recurrences which extended into the temporal bone
Mammary Analogue Secretory Carcinoma

• Recent series (Skalova et al, 2014) described high grade transformation in MASC
  – Cases were characterized as having 2 distinct components (typical MASC and high grade component) with abrupt transition
    • The high grade component was composed of anaplastic, pleomorphic nuclei with prominent nucleoli arranged in trabeculae

• Necrosis, desmoplastic stromal reaction, and perineural invasion were present

• No secretions were present
Mammary Analogue Secretory Carcinoma

- Ki-67 was increased compared to the low grade component (23% vs. 53%)
- P53 was positive in the high grade component, the high grade component also stained positive for DOG-1 in 2 of 3 cases
- ETV6 gene rearrangement was found in both the low grade and high grade components
- Has an aggressive clinical course, with 3 of 3 patients DOD
Mammary Analogue Secretory Carcinoma

• Differential Diagnosis
  – Acinic cell carcinoma
    • Most cases were originally diagnosed as zymogen granule poor acinic cell carcinomas
      – t(12;15) translocation is not present in ACC
      – PAS staining will show some intracytoplasmic zymogen granules
      – ACC is DOG-1 positive, mammaglobin negative
Mammary Analogue Secretory Carcinoma

• Differential Diagnosis
  – Mucoepidermoid Carcinoma
    • While MASC can have rare cells with intracytoplasmic mucin, no epidermoid or intermediate cell population of cells is present.
    • MASC have no or rare P63 positive staining and strong S-100 staining
    • MEC can have t(11;19) (CRTC1-MAML2) translocation, as opposed to the t(12;15) translocation of MASC
Mammary Analogue Secretory Carcinoma

– Adenocarcinoma/Cystadenocarcinoma, NOS

• The presence of characteristic morphologic and immunohistologic features of MASC should avoid misclassification as a NOS

• Presence of translocation can confirm diagnosis
Case #4

• 32 year-old female with a painful right submandibular gland mass.
Case #4

• Immunohistochemical staining
  – Portion of the neoplasm shows biphasic staining, with the majority of the cells positive for myoepithelial markers
  – Pan-CK stains highlight the ductal cells
  – High grade area is positive for pan-CK, but only focal areas with residual myoepithelial markers (p63, SMA, calponin) are present
  – P53 staining shows an increased staining pattern within the high grade component
Adenoid Cystic Carcinoma

- Accounts for about 5% of salivary gland tumors
- Parotid gland and minor salivary gland are most common sites
  - Minor salivary gland involvement account for about 50% of cases, with the palate being the most common site
- Peak incidence in the 6th decade, but a broad age range
  - Uncommon in pediatric population
- Slight female predominance
Adenoid Cystic Carcinoma

- Present as slow-growing masses, but can have facial nerve paralysis and pain
  - Perineural invasion is common
- Fixation to overlying skin may be present
- Intraoral tumors may have mucosal ulceration
- On gross examination, the tumors appear infiltrative, lacking a capsule, with a firm, white to gray appearance
Adenoid Cystic Carcinoma

• Prolonged clinical course with multiple local recurrences, late onset of distant metastatic disease
  – 5 year survival –75%
  – 15 year survival – 35%

• Often have positive margins due to propensity for perineural invasion
Adenoid Cystic Carcinoma

• Biphasic neoplasm composed of myoepithelial and ductal epithelial cells arranged in 3 main patterns:
  – Tubular
  – Cribriform – most common
  – Solid
  – Usually a mixture of patterns is present
Adenoid Cystic Carcinoma

- Myoepithelial cells predominate and have monotonous, round-oval shaped to angulated nuclei which may be lightly basophilic to hyperchromatic
- The cytoplasm is usually scant and is lightly eosinophilic to clear
- The less numerous ductal cells appear cuboidal with eosinophilic cytoplasm and round, regular nuclei
Adenoid Cystic Carcinoma

• Have blue-tinged secretions and/or brightly eosinophilic basement membrane material
  – Basophilic secretions are Alcian blue positive
  – Basement membrane material is PAS positive

• Stroma appears myxoid to hyalinized and can be extensive, with only compressed tubular structures

• Metaplasia (squamous, sebaceous, etc.) are characteristically absent in adenoid cystic carcinomas
Adenoid Cystic Carcinoma

• Cribriform pattern
  – Nests of cells with small, round, pseudocyst formation, which are not true glandular-lined cysts, but multiple small stromal or secretion-filled spaces
  – Rare, small true glandular lumens lined by cuboidal epithelial cells are present within the nests, but are often difficult to locate
Adenoid Cystic Carcinoma

- Tubular pattern
  - Lumens are lined by ductal epithelial cells with abluminal layer of myoepithelial cells
  - May appear compressed into strands in the presence of abundant stroma
Adenoid Cystic Carcinoma

• Mitotic figures are not readily identified, especially in the tubular and cribriform patterns
  – The solid pattern has more frequent mitotic figures (5/10 hpf)

• While necrosis is uncommon in tubular and cribriform areas, it is often present in the solid areas

• Solid areas are also characterized by larger cells and more pleomorphism
Adenoid Cystic Carcinoma

• Immunohistochemical profile
  – Ductal cells – positive for CK7, CAM 5.2, EMA, and stain more intensely with pan-CK
  – Myoepithelial cells – positive for CK 5/6, p63, SMA, calponin
  – CD117 is positive and preferentially stains the ductal component
  – S-100 shows variable staining in both populations
Adenoid Cystic Carcinoma with High Grade Transformation

• Adenoid Cystic Carcinoma with high grade transformation tend to occur during or after the 6th decade of life and have a slight male predilection

• Most common sites are the sinonasal glands, minor salivary glands, and submandibular glands
Adenoid Cystic Carcinoma with High Grade Transformation

• Although the mean size is only 3 cm, tumors are commonly at a high stage at presentation, with extraglandular extension and bony invasion

• Lymph node metastasis more common than conventional adenoid cystic carcinoma
  – Lymph nodes are positive in approximately 55% of cases, compared to 5-25% in conventional adenoid cystic carcinoma
Adenoid Cystic with High Grade Transformation

• In general, behave more aggressively than conventional adenoid cystic carcinomas
  – Median overall survival varies from 36 months to 12 months, depending on the study
  – Compared to median overall of solid adenoid cystic carcinoma, which is 3 years
Adenoid Cystic Carcinoma with High Grade Transformation

• Defined as the presence of poorly differentiated carcinoma/undifferentiated carcinoma juxtaposed to conventional adenoid cystic carcinoma

• Usually found adjacent to high grade adenoid cystic carcinoma, but at times can be present adjacent to lower histologic grade tumor

• Abrupt transition is common, but can have gradual transformation

• Percentage of component that is high grade transformation can vary, but is usually a large proportion (average 70% in Seethala et al.)
Adenoid Cystic with High Grade Transformation

- Characterized by:
  - Nuclear enlargement (>2-3 x normal) and prominent nuclear membrane irregularity
  - Increased mitotic activity
  - Loss of biphasic differentiation

- The cells have enlarged, vesicular nuclei with prominent nucleoli and moderate amounts of cytoplasm arranged in solid and cribriforming sheets of cells
Adenoid Cystic Carcinoma with High Grade Transformation

- May have areas of micropapillae or squamoid appearance
- Necrosis is present, often in large, confluent areas and may have associated microcalcifications
- The stroma has a desmoplastic reaction
Adenoid Cystic Carcinoma with High Grade Transformation

• Immunohistochemical profile
  – Positive for CK, EMA, and S-100
  – Myoepithelial/basal markers (p63, SMA, calponin)
    • Can have areas with scattered positive staining, but at least focal areas should have complete absence of staining
  – P53 staining is often increased in comparison to the adjacent conventional adenoid cystic carcinoma, usually showing strong positive staining in > 50% of the cells
  – Ki-67 is increased over the adjacent conventional adenoid cystic carcinoma (>50% positive)
HGT vs. Solid Pattern

- Solid pattern can have necrosis, nuclear enlargement, and an increase in mitotic figures when compared to tubular/cribriform patterns of adenoid cystic carcinoma.
- Unlike HGT, the necrosis is solid pattern is usually focal and punctate, and lacks associated microcalcifications.
HGT vs. Solid Pattern

- The nuclear enlargement in solid pattern ACC is at most 2x the size of nuclei in the tubular/cribriform areas and appear monotonous as opposed to the HGT nuclei which are 2-3 x enlarged and have pleomorphism
- Overlapping mitotic rates are present, but in general HGT has increased mitotic rates
  - In Seethala et al. solid pattern ACC had an average of 3.5 mitotic figures/10 hpf (range 0-11), while the HGT areas had an average of 17/10 hpf (range 5-67)
HGT vs. Solid Pattern

- The architectural pattern are different as well, with HGT have broad solid sheets of cells while the solid areas in the solid pattern of ACC are usually smaller nests with intermixed tubular and cribriform patterns of ACC
  - The HGT areas may have micropapillary and squamoid areas, which are not present in solid pattern ACC
- The stroma in HGT appears desmoplastic as opposed to the hypocellular myxoid or hyaline stroma of conventional solid pattern ACC
- IHC – solid pattern of conventional ACC has population of myoepithelial cells, as opposed to HGT areas
Adenoid Cystic with High Grade Transformation

• Differential Diagnosis
  – Essentially that of poorly differentiated blue cell tumors in the region
    • Basaloid squamous cell carcinoma
      – Basaloid SqCC are diffusely P63 positive, unlike AdCC which are predominantly negative
      – Basaloid SqCC may have adjacent dysplasia or CIS or the mucosal surface
      – Basaloid SqCC have peripheral palisading of the cells and the pleomorphism is more extensive
    • Neuroendocrine carcinoma
      – Synaptophysin and chromogranin
Special Thanks

• Dr. Raja Seethala
• Dr. Ericka Olgaard
References

References