FNA Diagnosis of Challenging Salivary Gland Neoplasms

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Salivary Gland FNA

- Fine needle aspiration (FNA) is a well-established diagnostic approach for salivary gland lesions
- Safe, minimally invasive, rare complications
- Rapid assessment and initial triage
- Guides preoperative strategy
  - Superficial parotidectomy vs
  - Total parotidectomy with facial nerve sacrifice +/− LN dissection
- Provides material for ancillary studies

Salivary Gland FNA Challenges

- Diversity of histologic subtypes (45 primary salivary gland tumors including many rare entities)
- Overlapping cytomorphology between benign and malignant tumors
- Inability to capture histologic architecture (cell blocks provide additional advantage)
- Indeterminate interpretation despite cellular adequacy
- No standard terminology for reporting salivary gland FNA as of now
  - The Milan system for Reporting Salivary Gland Cytopathology

Salivary Glands

Three major salivary glands:
- Parotid (entirely serous)
- Submandibular (more serous)
- Sublingual (more mucinous)

Minor salivary glands (upper aerodigestive submucosa) are variably mucinous and serous

There are 5-10 lymph nodes in each parotid gland
Submandibular and sublingual glands have no lymph nodes
Normal Salivary Gland Aspirate

- Bloody, mildly cellular and painful

Normal Triad

1. Acinar cells
2. Ductal cells
3. Fibroadipose tissue

Salivary Gland Tumors

- Majority are benign
  - Pleomorphic adenoma and Warthin tumor comprise over 80% of total salivary gland tumors
- Most occur in the parotid gland
- Among minor glands, the palate is the most common site for neoplasia
- Most malignant tumors are low grade

Parotid Gland Tumors

- Majority of parotid gland tumors develop within the superficial lobe
- Tumors originating within the deep lobe of the parotid gland usually present as pharyngeal swellings due to expansion into the parapharyngeal space

Normal Salivary Gland Aspirate

- The malignant lesions most often diagnosed as benign:
  - Misdiagnosis of low-grade malignancy:
    - Lymphoma (MALToma)
    - Acinic cell carcinoma
    - Low-grade mucoepidermoid carcinoma
    - Adenoid cystic carcinoma
- The benign lesions most often diagnosed as malignant:
  - Basal cell adenoma
  - Intraparotid lymph node
  - Oncocytoma
Case

- A 64 year old female with a history of melanoma and 0.6 x 0.5 x 0.5 cm left parotid gland lesion
- FNA was performed and cytologic diagnosis rendered at OSH: WARTHIN TUMOR
Case

- The patient underwent surgical resection
- Ill-defined, semi-firm, grey-tan and red 0.7 cm nodule in the parotid gland
Case

- Surgical Resection Diagnosis:
  - SALIVARY DUCT CARCINOMA

Oncocytoma/Oncocytic carcinoma
- Warthin tumor
- Oncocytic variant of mucoepidermoid carcinoma
- Pleomorphic adenoma with oncocytic features
- Salivary duct carcinoma
- Acinic cell carcinoma
- Metastatic carcinoma (renal cell carcinoma)

Salivary Duct Carcinoma
- First described in 1968
- Adenocarcinoma, usually high-grade, can be low-grade
- 9% of all malignant salivary gland tumors
- Major salivary glands (parotid)
- Resembles in situ and invasive ductal carcinoma of the breast
- May arise in a pleomorphic adenoma
Salivary Duct Carcinoma

- Often rapid growth
- Patients 40 years and above (average age 60 years)
- Much more common in men (4:1)
- Poor prognosis (5 year survival <35%)

Salivary Duct Carcinoma - Cytologic Features

- Large polygonal cells with abundant vacuolated or oncocytic cytoplasm
- Can show cribriform, papillary, and sheet-like cellular arrangements
- Single cells
- Prominent central macronucleolus
- Necrosis with “dirty” background

Salivary Duct Carcinoma - Immunohistochemistry

- ANDROGEN RECEPTOR positive (90%)
- HER2 positive
- GCDFP-15 positive in most tumors
- Other ductal markers (CK7, CEA) positive
- Rarely positive for ER and PR

Salivary Duct Carcinoma - Cytologic Differential

- High-grade mucoepidermoid carcinoma and carcinoma ex-pleomorphic adenoma
- Oncocytic neoplasms (Warthin tumor)
- Acinic cell carcinoma
- Metastatic tumors

Warthin Tumor

- Papillary Cystadenoma Lymphomatosum, Adenolymphoma
- 5-15% of all salivary gland neoplasms
- Second most common benign salivary gland neoplasm
- Malignant transformation to carcinoma or lymphoma is very rare

Warthin Tumor

- Almost exclusively located in the parotid
  Thought to arise from epithelial rests of salivary tissue entrapped within periparotid or infraparotid lymph nodes
- 50-80 years old
- Current or prior history of smoking (8 fold increased risk)
- Most common bilateral salivary gland neoplasm
- Cystic by definition
- Can be multifocal
- Soft on palpation
Warthin Tumor - Cytologic Findings

- Granular cystic background (composed of exfoliated degenerated oncocytes; rich in protein)
- Cohesive oncocytes in flat sheets
- No mitoses
- Lymphocytes, germinal center elements
- Pitfall: Mucinous or squamous metaplasia (occur in 30% tumors)

Warthin Tumor - Cytologic Differential

- Oncocytoma
  - No cystic change or prominent lymphocytes
- Acinic cell carcinoma
  - Bland cells with background lymphocytes
  - Can be cystic
  - BLUE COARSE GRANULES on H&E
- Salivary duct carcinoma

Salivary Duct Carcinoma vs Warthin Tumor

Salivary Duct Carcinoma
- Nuclei are ARCHITECTURALLY DISORDERED (nuclear overlap)
- Nuclear pleomorphism
- Mitoses/single cells

Warthin Tumor
- Tumor nuclei are UNIFORMLY SPACED
- Absence of nuclear pleomorphism
- No mitoses/no single cells

Our Experience

- Seven year retrospective search (2010-2016)
- 9 cases of histologically proven salivary duct carcinoma
- Average age 65 years; 78% male; all located in the parotid gland
- Initial cytologic diagnoses:
  - Salivary duct carcinoma (2 cases)
  - Intermediate to high-grade carcinoma (3 cases)
  - Mucoepidermoid carcinoma (1 case)
  - Oncocytic neoplasm (1 case)
  - Warthin tumor (2 cases)
Our Experience

- Oncocytic change was noted in all cases (33% moderate, 56% marked)
- Cellularity (22% moderate, 56% marked)
- Nuclear atypia (22% moderate, 11% moderate to marked, 22% marked)
- Prominent nucleoli (100%)
- Cytoplasmic vacuolation (11% moderate, 0% marked)
- Background necrosis (11% moderate, 33% marked)
- 3 of 9 cases (33%) exhibited cribriform architecture
- Foamy/cystic macrophages were noted in 5 of 9 cases (56%)
- None of the cases showed background lymphocytes

Key Points

- Salivary duct carcinoma cell cytoplasm can resemble oncocytes
- There is a potential for misdiagnosis as Warthin tumor
- In the differential diagnosis between salivary duct carcinoma and Warthin tumor rely on the architectural disorder and nuclear variability

Oncocytoma

- Benign neoplasm
- Less than 1% of all salivary gland tumors
- Rarely seen before age of 60
- The parotid gland is the most common site (80%)
- Solid tumor
- Oncocytic carcinoma (very rare; cytologic atypia)

Oncocytoma - Cytologic Findings

- Pure population of oncocytes (cohesive or discohesive)
  - Clear cell change may occur
- Densely granular cytoplasm without vacuoles
- Well defined cell borders
- Clean background or occasionally lymphocytes may be seen

Oncocytoma - Cytologic Differential

- Warthin tumor
  - Cystic background
  - Oncocytes appear smaller and less granular
  - Less cellular
- Acinic cell carcinoma
  - Delicate cytoplasm with small vacuoles
- Metastatic tumors (renal cell carcinoma)
Case

- 48 year old woman with a parotid gland mass
Acinic Cell Carcinoma

- Third most common salivary gland malignancy in adults
- Second most common salivary gland malignancy in children
- The most common bilateral malignant salivary gland tumor
- First described by D Nasse in 1892
- Was considered benign until RW Buxton et al reported 5 cases that behaved malignantly

Acinic Cell Carcinoma

- Most arise in the parotid gland (over 75% of all cases)
- Childhood to old age (average age 50 years)
- Female predominance (3:2)

Acinic Cell Carcinoma

- At least focal serous acinar differentiation
- Slow-growing tumor
- Usually well-moderately differentiated
- High grade transformation possible
  - Loss of blue granules
- Vulnerable to infarction following FNA
- Good prognosis, but subset may develop recurrent and/or metastatic disease (after decades)

Acinic Cell Carcinoma

- May be cystic, particularly papillary cystic variant

Acinic Cell Carcinoma

- Periodic acid-Schiff (PAS) positive, diastase resistant cytoplasmic zymogen granules
- DOG-1 positive
- No specific molecular changes have been identified

Acinic Cell Carcinoma-Cytologic Findings

- Bland cells with indistinct cell borders and abundant cytoplasm
- Zymogen granules and cytoplasmic vacuoles
- Background lymphocytes
- Bare tumor cell nuclei (fragile cytoplasm)
  - Not as small and dense as lymphocytes
- Large branching vessels may be seen
Acinic Cell Carcinoma - Key Cytologic Differential
- Normal parotid gland tissue
- Chronic sialadenitis
- Mammary analogue secretory carcinoma
- Metastatic clear cell renal cell carcinoma
  - Larger cells with foamy cytoplasm

Normal Salivary Gland vs Acinic Cell Carcinoma
- Less cellular
- Lobular arrangement
- Ducts present
- More cellular
- Acinic cells are haphazardly arranged
- Acinic cells only, no ducts or fibrofatty stroma

Mammary Analogue Secretory Carcinoma of Salivary Gland
- Described in 2010
- t(12;15)(p13;q25) translocation result in an ETV6-NTRK3 fusion
- Resembles secretory carcinoma of the breast histologically and immunohistochemically
- Cellular with sheets and clusters of uniform epithelial cells
- Mucoid material

Mammary Analogue Secretory Carcinoma of Salivary Gland
- S100 and mammaglobin positive
- Intracytoplasmic vacuoles and extracellular material are positive for mucin

Case
- 64 year old man with a left parotid gland mass
- FNA was performed
CD117 overexpression

Adenoid Cystic Carcinoma

- Second most common salivary gland malignancy
- Half arise in minor salivary glands (palate)
- Painful
- Rarely grossly cystic
- Slightly more common in women (5th decade)
- 5 year survival is >75%; 15 year survival is <35%
**Adenoid Cystic Carcinoma**

- Tubulocribriform or solid growth patterns
- Ductal epithelial and myoepithelial cells
- Basement membrane-like material in spaces is secreted by myoepithelial cells

**Adenoid Cystic Carcinoma-Key Cytologic Findings**

- Uniform basaloid cells with scant clear cytoplasm
- Dark angulated nuclei
- Metachromatic (magenta in Romanowsky, translucent in Pap stain), homogenous matrix material: globules or cylinders
- Solid pattern adenoid cystic carcinoma: basaloid cells with little to no matrix

**Adenoid Cystic Carcinoma-Cytologic Differential**

- Tumors with matrix and hyaline globules (pleomorphic adenoma, carcinoma ex pleomorphic adenoma, basal cell adenoma and adenocarcinoma, epithelial-myoeplithelial carcinoma, polymorphous low-grade adenocarcinoma)
  - The globules are often less numerous and smaller

**Pleomorphic Adenoma**

**Adenoid Cystic Carcinoma vs Pleomorphic Adenoma**

<table>
<thead>
<tr>
<th>Adenoid Cystic Carcinoma</th>
<th>Pleomorphic adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogenous stroma with smooth outlines</td>
<td>Fibrillar stroma with feathery outlines</td>
</tr>
<tr>
<td>Abundant hyaline globules</td>
<td>Sparse hyaline globules</td>
</tr>
<tr>
<td>Cells surround the stroma</td>
<td>Cells infiltrating the stroma</td>
</tr>
</tbody>
</table>
Basal Cell Adenoma - Tubulotrabecular & Membranous

Solid Variant Adenoid Cystic Carcinoma

Solid Variant Adenoid Cystic Carcinoma - Differential
- Basaloid neoplasms:
  - Cellular pleomorphic adenoma
  - Basal cells adenoma, solid subtype
  - Basal cell adenocarcinoma
  - Cutaneous basal cell carcinoma
  - Metastatic basaloid squamous carcinoma
- Often descriptive report with a differential diagnosis

Adenoid Cystic Carcinoma
- CD117 is strongly positive

Adenoid Cystic Carcinoma: Molecular Markers
- Translocation t(6;9), MYB oncogene-NFIB transcription factor fusion reported in the majority of adenoid cystic carcinomas
- Up-regulation of the MYB proto-oncogene

Low-Grade Mucoepidermoid Carcinoma
- The most common malignant salivary gland tumor in both adults and children in major and minor salivary glands
  - Parotid, palate, or buccal mucosa
- Middle age 50s
- Almost always cystic
- Correctly diagnosed in only 50% of cases
Low-Grade Mucoepidermoid Carcinoma - Cytologic Findings

- Abundant extracellular mucin
- Mucous glandular cells
  - May be mistaken for histiocytes
- Epidermoid (squamous) cells
- Intermediate cells
- Minimal atypia
- Sometimes only mucus, histiocytes and muciphages

Mucoepidermoid Carcinoma - Cytologic Differential

- Acquired non-neoplastic mucinous cysts
  - Mucocele, retention cyst
- Chronic sialadenitis
- Warthin tumor with mucinous metaplasia
  - Lymphocytes, oncocytes, granular debris
- Pleomorphic adenoma with mucinous change
  - Chondromyxoid stroma
- Mammary analogue secretory carcinoma
Any cystic salivary gland lesion containing mucinous background should suggest the low-grade mucoepidermoid carcinoma in the differential.

Mucoepidermoid Carcinoma
- Diffusely p63 positive

Low-Grade Mucoepidermoid Carcinoma
- Translocation t(11;19) (q21;p13) MECT1-MAML2 fusion
- This gene translocation occurs in more than 50% of mucoepidermoid carcinomas and shows significantly better survival than the fusion negative tumors

Low-Grade Mucoepidermoid Carcinoma - Treatment
- Low-grade tumors can be treated by local excision and the 5-year survival rate is about 98%
- Frequent local recurrences