Objective: To describe the use of FNA Bx to diagnose salivary gland lesions

Upon completion, participants should be able to:

- Survey the biopsy material to observe diagnostic clues
- Prepare a differential diagnosis based on observations
- Interpret the findings to arrive at a final diagnosis
- Transmit the diagnosis in a clinically meaningful way

SPIT out a diagnosis

Salivary Gland & FNA Biopsy

- Many diseases: Most diagnosable
- FNA Bx widely accepted: SAFE Simple, Accurate, Fast, Economic
- Diagnostic Problems
  - Cystic lesions (many are neoplasms)
  - Hyaline or mucinous material
Normal Salivary Gland

Major Salivary Glands: paired
- Parotid (Largest; + MALT)
- Submandibular
- Sublingual

Minor Salivary Glands
- Up to 1000
- Oral cavity & environs

Number neoplasms ~ Size of gland

Normal Morphology

Acini
Ducts
Fibroadipose Tissue

Salivary Gland

<table>
<thead>
<tr>
<th>Gland</th>
<th>Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid</td>
<td>Serous</td>
</tr>
<tr>
<td>Submandibular</td>
<td>Serous &gt; mucous</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Mucous &gt; serous</td>
</tr>
<tr>
<td>Minor</td>
<td>Variable</td>
</tr>
</tbody>
</table>
**Simple Diagnostic Algorithm**

Is the salivary gland lesion:
- Reactive (e.g., sialadenitis)?
- Or not (i.e., neoplastic)?

If neoplastic:
- Is it adenoid cystic carcinoma?
- Or not?

If not adenoid cystic carcinoma:
- Is it lymphoma?
- Or metastatic tumor?

**Salivary Gland Diseases**

1. Sialadenosis
2. Cysts
3. Inflammations
4. Neoplasia
   - Frequently cystic → FN!

**Sialadenosis**

Usually bilateral, nontender

Metabolic neuropathy (EtOH, malnutrition, etc)
- Large acini and acinic cells
  - as if magnified
- No inflammation
- No neoplasia

Biopsy may be painful!

DDx: Other bilateral conditions
- Lymphoepithelial sialadenitis,
- sarcoidosis, Warthin tumor, etc
Sialadenosis

...as if magnified

Salivary Gland Cysts
Many are neoplastic!

Nonneoplastic cysts
- Retention cyst
- Mucocele
- Lymphoepithelial cyst
- Cystic lymphoepithelial lesion
- HIV-associated cysts
- Cystic chronic sialadenitis
- DDx: cervical cysts, eg, branchial cleft cysts

Neoplastic cysts
- Benign
  - Warthin tumor
  - Pleomorphic adenoma*
  - Basal cell adenoma*
  - Papillary cystadenoma
  - Mucinous cystadenoma
- Malignant
  - Mucoepidermoid carcinoma*
  - Acinic cell carcinoma*
  - Cystadenocarcinoma
  - Cystic metastases (eg, SCC, PTC)
  *Some cases

Cysts

Neoplastic ‘til proven otherwise
To exclude cystic neoplasm:
- Drain the cyst
- Reaspirate residual mass
- Re-examine in 2 to 4 weeks and again in a few months ...to confirm resolution
- Excise if recurs > once
Nonneoplastic Cysts

Any gland; any age
Fluid (protein precipitate)
- Few cells, mostly macrophages
- Inflammation, crystals, debris
- Risky cysts: ↑ cells, ↑ atypia

Cystic neoplasms → false negatives
WARD* cells → false positives
*Worrisome Atypia in Reactive/Degenerative cells
Multiple bilateral cx cysts => R/O HIV

WARD Cells

Worrisome Atypia in Reactive/Degenerative Cells
Frequently associated with cysts, often have repair-like features

Suspicious Cysts

More cells; more atypia
Suspicious character
Sialadenitis

Classic clinical presentation:
- H/O acute or chronic, recurrent pain
- Swollen gland w/o distinct mass

Usually not a good candidate for FNA Bx
- Painful, yields little new information
- Material can be acquired for culture
- FNA bx for discrete mass, suspect neoplasia

Acute Sialadenitis

Diffusely enlarged, tender, oft parotid
- Viral: rarely see inclusions
  - Note: chronic inflammation!
- Bacterial: associated with stones
- Rarely bx unless abscessed (mass)
  - Neutrophils, fibrin, necrosis
  - ± Organisms (culture)
- DDx: WARD cells vs inflamed tumor

Chronic Sialadenitis

Diffusely enlarged firm gland (oft submandibular)
- Can form firm nodule, ~ neoplasm (Küttner tumor)
- IgG4-related sclerosing diseases
  - Often with autoimmune ds, eg, RA
- Histologic tetrad:
  1. Acinic atrophy
  2. Ductal metaplasia
  3. Chronic inflammation
  4. Fibrosis
Chronic Sialadenitis

- Painful, bloody aspirate*
- Few cells: Ductal > acinic
- Chronic inflammation variable
- Stromal fragments (~fibrosis)
  + Patchy, paradoxically normal FNA
  *vs neoplasm: ~painless, abundant material

Granulomatous Sialadenitis

- Sarcoid: noncaseating
  + Asteroid, Schaumann bodies
  Tuberculoid: caseating
  Cat-scratch, fungus: suppurative
  Toxo: baby granulomas
  Also: tumors, other rare causes

Autoimmune Sialadenitis

- Mikulicz disease: localized
- Sjögren syndrome: systemic
  + Rheumatoid arthritis (or other)
  High risk of lymphoma
- Autoimmune destruction
  of lacrimal & salivary glands →
- Sicca syndrome: dry eyes & mouth
- LESA*: painless bilateral enlargement
  *lymphoepithelial sialadenitis
Lymphoepithelial Sialadenitis

- Parenchymal atrophy, debris, protein ppt
- Metachromatic hyaline material
- Not specific for autoimmune sialadenitis

Salivary Glands in HIV

Salivary glands enlarged in ~5% HIV cases
- Cysts, inflammation, neoplasia
- Most = benign lymphoepithelial cysts, parotid
- HIV-related parotid cysts rarely malignant
- Suspect HIV infx: multiple, bilateral cx cysts
- Solid lesions also occur:
  - Inflammation vs neoplasia

Benign Lymphoepithelial Cyst in HIV Infection

- Multiple, bilateral parotid
- Clear to turbid fluid
- Foamy macrophages
- Lymphoid cells
- Epithelial cells (sparse)
  - squamous > glandular
- Protein ppt, mucus, crystals, etc
Salivary Gland Neoplasms

Salivary gland neoplasms are rare!

- Most neoplasms occur in parotid
- Most neoplasms are benign
- Most benign neoplasms are pleomorphic adenomas
- Most malignant neoplasms are mucoepidermoid carcinomas

Salivary Gland Neoplasms

<table>
<thead>
<tr>
<th>Location</th>
<th>% All Neoplasms</th>
<th>% Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Submandibular</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Sublingual</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>Minor</td>
<td>Rare</td>
<td>80</td>
</tr>
</tbody>
</table>

Number of neoplasms correlates directly with size of gland
Number of malignancies correlates inversely with gland size

Pleomorphic Adenoma (Mixed Tumor)

Most common salivary neoplasm: most in parotid
Benign, but recurs if incompletely excised
Remarkably varied morphology...

<table>
<thead>
<tr>
<th>Architecture</th>
<th>Epithelium</th>
<th>Myoepithelium</th>
<th>Stroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular</td>
<td>Mucinous</td>
<td>Spindle</td>
<td>Collagen</td>
</tr>
<tr>
<td>Cystic</td>
<td>Squamous</td>
<td>Epithelioid</td>
<td>Myxoid</td>
</tr>
<tr>
<td>Hyalinized</td>
<td>Oncocytic</td>
<td>Hyaline</td>
<td>Chondroid</td>
</tr>
<tr>
<td>Papillary</td>
<td>Sebaceous</td>
<td>Clear</td>
<td>Osteoid</td>
</tr>
</tbody>
</table>

...in infinite permutation
Pleomorphic Adenoma

Histology

Cytology

Cytodx usually straightforward
FNA Bx → glistening sticky gel
1. Epithelial cells
2. Mesenchymal cells
3. Stroma
Very variable proportions

Stroma

Fibrillar!

Metachromatic
A prize in every box…

- Cartilage
- Glandular cells
- Sebaceous cells
- Squamous cells
- Oncocytes
- Hyaline cells
- Various crystals
- Cytologic atypia
- Hyaline globules
- ...and more!

Cartilage

Also: osteoid or bone

Osteoclast

Osteoid or bone
Glandular Cells
DDx: Adenocarcinoma

Mucus or Goblet Cells
DDx: Mucoepidermoid CA

Intranuclear Cytoplasmic Invaginations (INCIs)
DDx: Papillary thyroid CA, or paraganglioma
Sebaceous Cells
DDx: Sebaceous or clear cell neoplasm; skin pick-up

Squamous Cells
DDx: SCC, MEC

Oncocytic Metaplasia
DDx: Warthin, Oncocytoma, MEC
Hyaline Cells

DDx: Plasmacytoma

Spindle Cells

DDx: Mesenchymal neoplasm

Adipose Tissue

DDx: Lipoma or geographic miss of the target (ie, subcutaneous fat)
Cystic Degeneration
Can lead to interpretive problems related to few cells or WARD cells

Tyrosine Crystals
Rare in other tumors

Collagen Crystals
Cytologic Atypia: WARD Cells

Atypical cells in benign pleomorphic adenomas
Usually sparse and randomly distributed
Diffuse marked atypia & necrosis favor malignancy

Adenoid Cystic-oid

Adenoid cystic carcinoma
Pleomorphic adenoma
Basal cell adenoma/CA
Warthin tumor
Oncocytoma
Acinic cell carcinoma
Epithelial-myoepithelial CA
Polymorphous low-grade CA
Skin appendage tumors

Spectrum

Basal cell adenoma

Pleomorphic adenoma

Myoepithelioma
**Basal Cell Adenoma**

Clinically ~ pleomorphic adenoma
Solid, tubular, trabecular, membranous
Basaloid cells
± Hyaline material
± Squamous differentiation
~ Fibromyxoid stroma of PA
DDx: Basal cell carcinoma (invasion)
Adenoid cystic CA (no squamous)
Nerve damage or cytologic atypia
=> malignant

**Trabecular Adenoma**

Cells embedded in hyaline stroma
...like kernels of corn on a cob
Basaloid cells + Hyalinized stroma
(variably metachromatic)
DDx: Adenoid cystic carcinoma

**Membranous Adenoma**

Dermal Analog Tumor (~Eccrine Cylindroma)

Thick bands of hyaline material
surround groups of basaloid cells
The hyaline material is
variably metachromatic
in Romanowsky stains
**Myoepithelioma**

Myoepithelial cells only  
No ductal differentiation  
- Spindle: delicate cytoplasm  
- Epithelioid: ~ epithelial cells  
- Hyaline: plasmacytoid, dense  
- Clear: glycogen  
Myxohyaline stroma  
Cytoatypia, mitosis, necrosis => malignant

**Warthin Tumor**

Parotid: ~ exclusively  
M ≈ F; >40, smokers  
Grungy crankcase oil fluid  
1. Oncocytes  
2. Lymphocytes  
3. Cyst content  
Mast cells
**Warthin Tumor**

WARD Cells:
- Atypical oncocytes
- Squamous metaplasia

DDx: Squamous cell CA

**Oncocytic Neoplasms**

Oncocytoma: rare
- Warthin tumor, except
- Oncocytes w/o lymphs
- Noncystic (solid) tumor
- Any salivary gland

Malignant cytology => carcinoma

**Adenoid Cystic Carcinoma**

2nd most common malignancy
- Also: lacrimal, sweat, breast, etc
- Slow, but relentless, growth
- Perineural invasion characteristic
- Lung, bone > node mets
- Basaloid cells: deceptively bland
- Hyaline globules: not specific!

*Do not diagnose unless clinically malignant!*
Adenoid Cystic Carcinoma

- Basaloid cells
- Hyaline globules

No: squamous, spindle, clear cells; fibrillar stroma; epithelial mucin

Most common salivary malignancy
Most occur in parotid
Low-grade: recurs; soft, cystic, painless
FNA Bx: cyst content, bland goblet cells

High-grade: mets; solid, symptoms
FNA Bx: ~ non-keratinizing SCC

Dx: gland + squamous cells (minimum)
Also: intermediate, clear, etc
Pearl: mucin (+) squamoid cells

Mucoepidermoid Carcinoma

Most common salivary malignancy
Most occur in parotid

Low-grade: recurs; soft, cystic, painless
FNA Bx: cyst content, bland goblet cells

High-grade: mets; solid, symptoms
FNA Bx: ~ non-keratinizing SCC

Dx: gland + squamous cells (minimum)
Also: intermediate, clear, etc
Pearl: mucin (+) squamoid cells
Acinic Cell Carcinoma

Most parotid, F > M, 40s
Most bilateral *malignant* tumor
Striking feature: late recurrences
- Serous acinic cells *only*
  - PAS (+) zymogen granules
- No normal ducts; no fatty stroma
- Lymphocytes

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Acinic Cell CA

Acini, Ducts, Fatty stroma
Acinic cells "only"
Malignant Mixed Tumors

1. Carcinoma ex pleomorphic adenoma (rare)
   CA arising out of pleomorphic adenoma
2. “True” malignant mixed tumor (rarer)
   Carcinosarcoma (CA + chondro-, osteo-sarc, etc)
3. “Benign” metastasizing mixed tumor (rarest)
   Benign morphology, not behavior

Recent rapid growth in longstanding nodule …suggests the diagnosis

Other Adenocarcinomas

- Salivary Duct CA: Very rare; aggressive, older men
  Similar to comedo breast CA
- Polymorphous LG AdCA: Minor glands, uniform myoepithelial or duct cells, metachromatic globules
- Epi-myoeapithelial CA: Parotid, older F; dark central epithelial cells + clear myoepithelial cells; metachromatic hyaline globules
- Basal Cell AdCA: Malignant counterpart basal adenoma
  Perineural invasion (DDx solid ACC)
- Mucus-producing AdCA: Adenocarcinoma
  small metachromatic globules
- Papillary AdCA: Papillae; psammomas, mucin; no squamous, intermediate, etc
- Mammary Analog Secretory Tumor
  t(12;15)(q13;q25) → ETV6-NTRK3 gene fusion; DOX = adenocanthoma
Salivary Duct Carcinoma

Aggressive tumor, older men
Stenson duct, parotid
Resembles ductal breast CA
High grade comedo necrosis
No hyaline globules
Androgen receptors, not ER, PR

Polymorphous Low-Grade AdCA

Minor salivary glands, older women
"Many forms" histologically
- Cells: bland epithelial cells + spindle myoepithelial cells
- Stroma: metachromatic matrix; hyaline globules
Branching pseudopapillae
DDx: Adenoid cystic CA

Epithelial-Myoepithelial CA

Parotid, older women
2-cell pattern
- Dark epithelial cells
- Light myoepithelial cells
+ Hyaline stroma
DDx: Adenoid cystic CA
**Mucinous Adenocarcinoma**

Adenocarcinoma ± small metachromatic globules

**Mammary Analog Secretory Tumor**

t(12;15)(q13;q25) → ETV6-NTRK3 gene fusion

(Secretory breast CA, infantile fibrosarcoma, mesoblastic nephroma)

Micro/macro cystic, sheets, papillae

Uniform cells; vacuolated cytoplasm; Histioctye-like

No matrix or spindle stromal cells; Mammoglobin +

DDx: Acinic cell CA (zymogen granules)


**Primary Squamous Cell CA**

Rare (~1% primary tumors)

2. SCC far more common

Dx: typical SCC, usually keratinizing

Mucin negative: if (+) => MEC

DDx: high-grade mucocystic CA

usually non-keratinizing
**Small Cell (Neuroendocrine) CA**

2 morphologic patterns:
- Merkel cell CA
  - better prognosis
  - CK20 dot (+)
- Small cell lung CA
  - more pleo, molding
  - Neuroendocrine markers (+)

DDx: Metastatic lung CA

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**Clear Cell Tumors**

Mixed bag, benign & malignant
- Myoepithelial adenomas, CAs
- Acinic cell CA
- Mucoepidermoid CA
- Sebaceous neoplasms
- Oncocytoma
- Metastatic CA (esp renal)
- Others

Hyaline material may occur

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**Malignant Lymphoma**

1 lymphomas:
- rare, but increasing
  - de novo
    - Large B cell lymphoma
  - LESA or Sjögren
    - MALTomas

Cytology depends on type
**Mesenchymal Tumors**

Rare (<3%), but any kind  
Most are benign; most in parotid  
- Hemangioma (blood)  
- Lipoma (fibroadipose)  
- Nerve sheath (spindle cells)

**Nerve Sheath Tumor?**

Dx: pleomorphic adenoma  
...with neural-like stroma

**Metastasis**

Not rare; most = SCC or melanoma  
→ intraparotid nodes  
DDx: Primary SCC (very rare)  
High-grade MEC (mucin [+] cells)  
Renal cell CA (mimics 1ª tumors)  
Immuno + clinical history!
Salivary Gland Masses in Kids

Most are inflammatory: viral, bacterial infection
Hemangioma: most common tumor (hamartoma?)
Pleomorphic adenoma: most common neoplasm
Mucoepidermoid CA: most common carcinoma
Rhabdomyosarcoma: most common sarcoma

Final Comment

There are many salivary gland tumors, ranging from benign to highly aggressive neoplasms, and they can look a lot alike.

Therefore, if the lesion does not fit neatly into one of the pigeon holes...BE CAREFUL!!!

Thank you