Role of Salivary Gland (SG) FNA

• to distinguish
  – a SG lesion from other H&N lesions/tissue
  – benign/l-g neoplasms from high-grade ones

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• guide patient management
  – identify lesions where surgery is not indicated
  – identify lesions where surgery may be indicated, but not necessary & patient followed clinically
Role of Salivary Gland (SG) FNA

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  - a SG lesion from other H/N lesions/tissue
  - benign/lg neoplasms from high-grade ones
- guide surgical management
  - identify lesions where surgery is not indicated
  - identify lesions where surgery may be indicated, but not necessary & patient followed clinically
- potential complications
  - bleeding/ infection/ facial nerve pain/ tumor seeding (rare)

709 cases (2 institutions), had both FNA + surgical excision
- benign v. malignant
  - sensitivity: 67.4% (not counting ‘atypical’ as ‘malignant’)
  - specificity: 98.9%
  - NPV: 91.8%
  - PPV: 94.1%
  - accuracy: 92.2%
- no statistical difference between LBC & conventional smears
- no cell blocks

Salivary Gland (SG) FNA

- SG tumors among the most heterogenous encountered in FNA practice

- pitfalls:
  - overlapping morphologic features
  - cystic change
  - metaplasia
    - clear cell/ squamous/ oncocytic/ and mucinous

Cancer 2016;124:388.
Role of Salivary Gland (SG) FNA

• to distinguish
  – a SG lesion from other H/N lesions/tissue
  – benign/l-g neoplasms from high-grade ones
• guide patient management
  – identify lesions where surgery is not indicated
  – identify lesions where surgery may be indicated, but not necessary & patient followed clinically
• render a specific Dx when possible
• complications
  – bleeding/ infection/ facial nerve pain/ tumor seeding (rare)

mediocre - poor performance of salivary gland FNA to provide specific diagnoses is well documented


Risk stratification scheme

<table>
<thead>
<tr>
<th>category</th>
<th>overall ROM</th>
<th>entities</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-diagnostic</td>
<td>2%</td>
<td>cyst contents</td>
</tr>
<tr>
<td>benign</td>
<td></td>
<td>non-neoplastic, PA, Warthin tumor</td>
</tr>
<tr>
<td>NUMP</td>
<td>18%</td>
<td>• monomorphic cellular basaloid neoplasm (MCBN) - with fibrillar stroma - with hyaline stroma • monomorphic oncocytoid neoplasm (MON) - with cyst contents bkgd. - with other bkgd.</td>
</tr>
<tr>
<td>suspicious</td>
<td>79%</td>
<td>• MC BN with mixed/other stroma • MON with mucinous bkgd. • cellular basaloid neoplasm with coarsely granular/vacuolated cytoplasm</td>
</tr>
<tr>
<td>malignant</td>
<td>100%</td>
<td>• pleomorphic basaloid neoplasm • pleomorphic oncocytoid neoplasm</td>
</tr>
</tbody>
</table>
### SG FNA – proposed Milan system

<table>
<thead>
<tr>
<th>Category</th>
<th>ROM</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-diagnostic</td>
<td>10-20%</td>
<td>repeat FNA vs. clinical F-U</td>
</tr>
<tr>
<td>non-neoplastic</td>
<td>TBD</td>
<td>clinical F-U/radiologic correlation</td>
</tr>
<tr>
<td>AUS</td>
<td>TBD</td>
<td>TBD</td>
</tr>
<tr>
<td>neoplasm</td>
<td>5-7%</td>
<td>conservative surgery vs. clinical F-U</td>
</tr>
<tr>
<td>benign</td>
<td>20-40%</td>
<td></td>
</tr>
<tr>
<td>uncertain malignant potential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>suspicious</td>
<td>70-80%</td>
<td>surgery</td>
</tr>
<tr>
<td>malignant</td>
<td>85-95%</td>
<td>surgery</td>
</tr>
<tr>
<td>• low-grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• high-grade</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Functional classification - primary lesions

- non-neoplastic conditions
- stromal dominant lesions
- oncocytic dominant lesions
- non-oncocytic cyto-B lesions
- cyto-M dominant lesions
- spindle cell dominant lesions
- basaloid dominant lesions

### Functional classification - primary lesions

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- basaloid dominant lesions

Specific Dx:
- U = usually; S = sometimes; D = descriptive
- U: inflammatory
- U: PA, AdCCA, S: l-g MEC
- U: WT. S: oncocytoma
- S: acinic cell, MASC
- S: adenoCA, SDC, h-g MEC
- D: myoepitheloma/CA, NF
- D: BCA/adenoCA, AdCCA solid, Ep/Myoepithelial CA, PLGA, clear cell CA
Normal SG

- normal parotid – cell slice
- normal parotid – smear
- rounded grape-like clusters
Non-Neoplastic Lesions

- sialadenitis
  - acute/chronic/granulomatous
- cysts
- sialosis
Acute Sialadenitis

Acute sialadenitis

Acute sialadenitis with crystalloids
SG Non-Tyrosine (amylase) Crystalloids

- 31 cases
- 30-86 yrs; F:M, 1:2:1
  93% = parotid
- FNA smears:
  - background neutrophils, proteinaceous debris
- histology in 36%:
  - cyst, sialolithiasis and sialadenitis, WT, cystadenoma, cellular PA
- crystalloids were not seen with any malignant lesion


Chronic Sialadenitis

- benign inflammatory process clinically simulating a neoplasm
- almost exclusive to the submandibular gland
- middle aged patients
- smears: low cellularity, scattered ducts with few acini, lymphoplasmacytic cells

Küttner 'tumor'

parotid: granulomatous sialadenitis
Functional classification
- primary lesions
  • non-neoplastic conditions
  • stromal dominant lesions
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Stromal/Matrix Dominant Lesions

PA
Adenoid Cystic CA
Polymorphous AdenoCA [PoA]
L-G MEC

Pleomorphic Adenoma

• most common SGT
  • >70% of all parotid tumors
• cytomorphology
  - variable cellularity
  - fibrillar chondromyxoid stroma
  - cells merge with stroma
  - variable cell shape:
    - polygonal, plasmacytoid, spindle, stellate
  - nuclei: round, slight anisokaryosis
  - cytoplasm
    • moderate, fine granular
• t(3;8) [upregulation of PLAG1] in 50-60% of cases
enormous amount of matrix

fibrillar edges

Myoepithelial Cells – ‘plasticity’

- Spindle
- Plasmacytoid
- Stellate
- Columnar
- Polygonal
- Clear Cell
- Basaloid
spindle/stellate

PA: spindle cells

melan
stellate & spindled

plasmacytoid/hyaline

The hyaline cell: a distinctive feature of 'mixed' salivary tumours

J.D. LOMAX-SMITH & J.G. AZZOPARDI*
Department of Histopathology, Royal Postgraduate Medical School, DuCane Road, London W12 OHS

Histopathology 1978, 2, 77-92

"cells have a generally eccentric nucleus, & a homogeneous, ground glass or hyaline eosinophilic cytoplasm"
PA- confusing cytologic variations

- minimal-to-no stroma [cellular PA vs. myoepithelioma]
- nuclear atypia [nucleomegaly]
- non-fibrillar stroma
- metaplastic changes [mucinous, clear cell, squamous]
- necrosis
PA: nuclear atypia

72 y/o ♂; PA, non-fibrillar stroma

Non-fibrillar stroma: PA or AdCCA??
PA ???

Adenoid Cystic CA

both PAs ???
Pleomorphic Adenoma

Adenoid Cystic CA

cribriform

both PAs ???
Pleomorphic Adenoma
forms of metaplasia

- squamous
- sebaceous
- oncocytic

- mucinous bkgd.
- clear cell

- epithelial stromal interdigitation and transition from epithelial to spindle cells

mucinous PA
mucinous PA, CB
infarcted PA – squamous CA?
Case

- 16 year old girl
- painless 2.2 cm. R parotid mass, unknown duration
- otherwise well; no relevant medical history
- FNA biopsy performed
PA – squamous metaplasia

PA – take home messages

- **most** cases have fibrillar stroma/matrix
- BUT, don’t just look at the matrix
  - it may have a smooth sharp contour/ globules
  - always look at the cells
    - plasmacytoid – typically with more cytoplasm than seen in AdCCA
    - spindle
- infarction & metaplasia happen
Cytologic Features ≠ Dx of PA

- cells in tubular/acinar formation, or finger-like branching
- absence of chondromyxoid stroma
- mucus-secreting cells
  - especially if readily identifiable/numerous
- large numbers of bare nuclei
- marked pleomorphism

Adenoid Cystic CA

- 4-10% SGT
- 4th–6th decade
- cytomorphology
  - basaloid cells with rounded oval nuclei without visible nucleoli
  - matrix: generally spherical or elongated with a glassy character
  - matrix: sharp smooth border surrounded by cells with little merging of cells into stroma
- t(6;9) MYB overexpression, 60%
- CD117, MYB, SOX-10 +
SGT With Cribriform Pattern

- Adenoid Cystic Carcinoma
- Focally Present
  - PA
  - basal cell adenoma
  - polymorphous adenoCA [PGA]
  - epithelial / myoepithelial CA
  - salivary duct carcinoma
Polymorphous AdenoCA (aka PLGA)

- almost exclusive to minor SG
  - 60% palate
- histopathology
  - cytologic uniformity with architectural diversity
- cytology
  - tubules, cords, linear groups
  - bland isomorphic oval nuclei
  - variable matrix
  - clean background

Polymorphous AdenoCA (PoA)

- IHC positive
  - p63, pan-CK, S-100, vimentin
- IHC negative
  - p40
- IHC usually negative
  - calponin, SMA, GFAP
- IHC variable
  - CD117
Case

- 79-year old man
- 0.7 cm. R pre-auricular nodule x 2 weeks.
- history of lymphoma diagnosed >20 years ago
Diagnosis?

How would you classify?

- Benign
  - macrophages & mucin

- Mucinous Lesion

- Malignant Mucinous Neoplasm

- Unsatisfactory:
  - cyst contents: macrophages & mucin

Which one?

- Benign
  - macrophages & mucin

- Mucinous Lesion

- Malignant Mucinous Neoplasm

- Unsatisfactory:
  - cyst contents: macrophages & mucin

Which one?
L-G MEC: abundant mucin

Low-Grade MucoEp CA

- most common mal. SGT
  - 30% of all major/minor SGT
- 40% outside major SG:
  - palate, buccal mucosa, lip
  - upper/lower resp. tract
- 80% low-grade
- wide age range

CRTC1-MAML2 fusion
- t(11;19) (q14–21; p12–13), 1st described in 2003
- 40-70% of MECs
Low-Grade MucoEp CA

  – FN rate = 43%
• cytomorphology
  – variable bkgd. mucin
  – cell clusters/sheets
  – monotonous rounded/oval nuclei
  – vacuolated cells
  – ± oncocytic change
  – keratinized cells

• D Dx when only extracellular mucin
  – mucus retention cyst
  – mucinous metaplasia
  • chronic sialadenitis
  • sialolithiasis
  • Warthin tumor
  • pleomorphic adenoma
  – metastatic mucinous neoplasm

intermediate cells
bland intermediate cells

L-G MucoEP CA

67 y/o ♀ L parotid
Oncocytic Dominant Lesions

WT
Oncocytoma
Oncocytic SG Neoplasms

Warthin Tumor

• A.S. Warthin 1929
  – "adenolymphoma",
  – "papillary cystadenoma lymphomatosum"
• 2nd most common SGT
• parotid
• White >> Asian, Hispanic, African
• one of the few SGT with M > F
• association with cigarette smoking
Warthin Tumor

WT: discrete nucleoli

Warthin Tumor
WT: acutely inflamed cell-block
Sources of diagnostic error in the fine-needle aspiration diagnosis of Warthin's tumor and clues to a correct diagnosis.

- 16 cases, WT
- oncocytic epithelium: abundant = 81%
- necrosis/debris: abundant = 56%, scant = 19% [75%]
- squamous cells: abundant = 25%, scant = 38%

WT–squamous metaplasia

43 y/o ♂ parotid mass

43 y/o ♂ mucinous WT
WT: Cause of Error *Cancer* 2003;99:166.

- paucity or lack of characteristic WT morphologic features
- overabundance of 1 or more of:
  - atypia
  - mucoid material / mucinous background
  - spindle shaped cells
  - cystic / necrotic / inflammatory debris

Oncocytoma

- many mistaken as WT
  - 15 cases in our files
    - 7 called Oncocytoma
    - 4 called WT
    - 3 called WT vs. Oncocytoma
    - 1 salivary gl neoplasm
- cytomorphology
  - sheets/cluster/single forms
  - large polygonal cells
  - voluminous cytoplasm
    - finely granular
  - smooth, rounded nuclei
    - small single nucleoli
  - clean background
Oncocytoma

54 y/o ♂ parotid mass
dx = oncocytic neoplasm

dx = oncocytic neoplasm
subsequent surgery, 1 mos. later

OMEC. recurrence 1.5 yrs. later

Non-Oncocytic Cytologically Bland Lesions

Acinic Cell CA
MASC
Epi/Myoepithelial CA
Acinic Cell Carcinoma [AciCC]

• 2-6% SGTs
• age: peak 40-45 yrs.
• sites: parotid – 90%, lip, palate
• histologic subtypes:
  – solid, microcystic, papillary cystic, follicular
• slow growing; metastases late
• SOX10, DOG-1 +
• no specific molecular marker

• cytomorphology
  – monotonous acinar cells
  – loose clusters
  – lack acinar/bunch of grapes’ architecture
  – single cells
  – cytoplasm vacuolated, basophilic granules
  – ill-defined or sharp cell borders
  ± oncocytic change
  ± lymphocytic infiltrate
  no matrix
Oncocytic SGTs

routinely & diffusely oncocytic

- Warthin T
- Oncocytoma

focal/infrequently oncocytic

- MucoEp CA
- Acinic CC
- Secretory CA [MASC]
- Salivary Duct CA

Oncocytic SGTs

Acinic CC

- SOX-10 +
- DOG-1+
- p63 negative

WT, oncocytoma, MEC

- SOX-10 negative
- DOG-1 negative
- p63 +
  - diffuse in MEC
  - focal in WT, oncocytoma

Secretory CA (MASC)

- parotid/extra-parotid sites
- cytomorphology: resembles Acinic Cell Carcinoma (AciCC) lacking cytoplasmic granules
  - cytoplasmic vacuoles
  - monotonous rounded nuclei
  - small distinct nucleoli
  - proteinaceous background
  - ± oncocytic change
- IHC
  - S-100, GATA3, mamm +
- specific molecular alteration
  - t(12;15)(p13;q25), ETV6-NTRK3 fusion

MASC: loose clusters, single cells

secretory proteinaceous background

vacuoles
Epithelial-Myoepithelial CA
- <1% of all SGTs
- >70% parotid; F:M = 2:1
- locally aggressive
- 2 cell types
  - luminal epithelial
  - abluminal myoepithelial cells
- clear cell change
- IHC + for myoepithelial markers

Epi/Myo CA - cytomorphology
- highly cellular smears
- 3-dimensional clusters
- single cells
- cellular monotony
- bare nuclei
- acellular basement membrane-like material
  - sometimes concentric balls/spheres
Cytologically Malignant (i.e. large/pleomorphic) Neoplasms

- Salivary Duct Ca
- H-G MEC
- Papillary Cystadenocarcinoma
- CA ex PA
Salivary Duct Carcinoma

- Kleinsasser et al., 1968
- tumors resembling ductal CA of breast
- 50-70 yrs. of age
- M >> F; 4:1

- sites: parotid (70%), submandibular, sublingual, minor salivary glands
- aggressive neoplasm
  - 50% distant mets
Salivary Duct Carcinoma - IHC

- Positive
  - cytokeratin
  - androgen receptor
  - EMA
  - CEA
  - ERBB2 (HER-2/neu)
- Negative
  - ER/PR
  - myoepithelial markers
  - Mucin

High-Grade MEC
(Papillary) Cystadenocarcinoma

- rare
- major SG: parotid (70%)
- papillary/cystic
- cells: mucinous, clear, oncocytic
- slow growing
- cytopathology
  - papillary clusters
  - variable mucinous bkgd.
  - monotonous smooth nuclei
Spindle Cell Lesions

Myoepithelial Neoplasia
Nodular Fasciitis
Schwannoma

Myoepithelial Neoplasia

- ~ ½ occur in parotid
- mimics cellular PA
- cytomorphology
  - clusters/single cells
  - primarily spindle; also stellate, plasmacytoid
  - isomorphic
  - variable amount of cytoplasm
  - clean background
  - ± collagen

myoepithelioma: plasmacytoid
40 x W. parotid tail

same case

myoepithelioma: spindle cell
Basaloid Lesions

- Basal Cell Adenoma
- Basal Cell Adenocarcinoma
- Adenoid Cystic CA

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U: WT, S oncocytoma
S: acinic cell, MASC
S: adenoCA, SDC, h-g MEC
D: myoepitheloma/CA, NF
D: BCA/adenoCA, AdCCA solid, Epl/Mesoepi CA, PLGA, clear cell CA
Basal Cell Neoplasia

- 2-3% all SGT
- ♀:♂ = 2:1
- 75% parotid
- Histologic patterns
  - solid, trabecular, tubular, membranous
- Cytopathology
  - irregular sheets basaloid cells, variable stroma, ± palisading
- Myoepithelial markers +

55 y/o ♀ parotid, basal cell adenoma

Ddx: cellular PA, BCA, AdCystic CA

Tubulotrabecular pattern
Functional classification - *primary* lesions

- non-neoplastic conditions
- *stromal* dominant lesions
- *oncocytic* dominant lesions
- *non-oncocytic* cyto-B lesions
- cyto-M dominant lesions
- *spindle cell* dominant lesions
- *basaloid* dominant lesions
References


• Tyagi et al. Diagn Cytopathol 2015; 43:495.