Topics

- Non-lymphoid Small Cell (cytoplasmic-poor)
- Non-lymphoid Large Cell (cytoplasmic-rich)
- Cystic
- Spindle cell

when it comes to FNA, the ‘neck’ is a BIG place

- thyroid
- parathyroid
- salivary gland
- paraganglia
- soft tissue
- lymph node
- larynx/trachea
Small Rounded Cell Lesions (cytoplasmic-poor)

D DX
- basaloid SqCCA
- small cell NEC
- ONB
- NUT midline CA
- malignant melanoma
- pilomatrixoma (PMX)
- alveolar RMS
- ameloblastoma
- adenoid cystic CA
- Merkel cell CA

Case 1
- 53 y/o ♂ presents with a 2.5 cm. right neck mass for an unknown period of time.
- no pertinent history.
case 1: neck mass
Diagnosis =

• ? metastatic adenoid cystic CA
• ? metastatic small cell NEC
• ? metastatic basaloid SqCC
• ? metastatic melanoma, small cell variant
Basaloid Squamous Cell Carcinoma

case 1

Basaloid SqCCA, Clinical

- 1986, Wain et al. (Hum Pathol 1986;17:1158)
- 6-8th decades; M > F, about 4:1
- sites:
  - oropharynx
  - larynx
  - sinonasal tract
- sx: hoarseness, dysphagia, neck pain, mass
- can be HPV-associated
- behavior: high grade neoplasm
a “basaloid” phenotype is seen in both HPV-positive and HPV-negative squamous carcinomas.

HPV status cannot be predicted from the histopathology (location, location, location)

D Dx, H/N basaloid SqCC

* ? metastatic basaloid SqCC
* ? metastatic small cell NEC
* ? metastatic adenoid cystic CA
* ? metastatic melanoma, small cell variant
small cell NEC

basaloid SqCC

'blue bodies'
D Dx
- ? metastatic basaloid SqCC
- ? metastatic small cell NEC
- ? metastatic adenoid cystic CA
- ? metastatic melanoma, small cell variant

Basaloid SqCC
- involves lower neck nodes
- + IHC: p63, p40, CK 5/6, 34βE12
- if esophageal, p16 nearly always diffusely +

Adenoid cystic CA
- involves upper neck nodes
- + IHC: myoepithelial markers, CD117, MYB
- p16 may be focally +
Our study found that the presence of adenoid cystic-like features and single keratinized cells were features specific for basaloid squamous cell carcinoma (p < 0.05).

Aspirates from adenoid cystic carcinoma are less likely to exhibit nuclear pleomorphism and necrosis.

Dx = 'Infiltrating Adenoid Cystic CA.

The biopsy received shows mostly the collagenous stroma and infiltration by neoplastic AdCC.'
FNA performed after transfer, but before outside slides reviewed
51 y/o man. Right neck lymph node, CNB.

FNA Ds = Adenoid Cystic CA

CK 5

p63

SMA

p40

HPV-Related SqCCA, basaloid (p16 also +)

p16

CK 5

SMA
case 2

my initial thoughts: if parotid, myoepithelioma?
myoepithelial CA

cytoplasmic processes
cytoplasmic processes

CB: non-keratinizing Sq.CA

high-risk HPV ISH
Non-keratinizing SqCC vs. Basaloid SqCC

- smooth-edged nests
- little-no stromal reaction
- oval-spindle nuclei, indistinct nucleoli
- comedo-necrosis
- squamous foci absent or < 10% of tumor area – patchy
- uncommon outside the oropharynx

- irregular nests/’jigsaw’ pattern
- cribriform-like stromal hyalinization
- nuclei round – oval; rarely with spindle forms
- ± comedo necrosis
- squamous foci are focal, ‘abrupt’
- not uncommon outside the oropharynx

Head/Neck Pathol 2012; Suppl. S41-47.
• HPV assessment recommended by Am. Joint Cmte on Cancer for Oropharyngeal CA.

• as many as 12,000 new cases of HPV-related Or-Ph SqCC reported yearly '04 to '08 in US1

• HPV-related SqCC has ↑by ≈ 225% in past 20-30 yrs while typical H/N SqCC has ↓by ≥ 50%2

• all O-P cancers should be tested for p16 AJCC manual 8th ed.


Oropharynx
not the same as oral cavity

- base of tongue
- lingual tonsil
- tonsillar fossa
- tonsillar pillars: anterior & posterior
- inferior surface of soft palate
- vallecula
- glossotonsillar sulci
- pharyngeal tonsils
- lateral & posterior pharyngeal walls
- uvula

plane extending from superior surface of soft palate to superior surface of hyoid
Clinical value of HPV status

- 3 yr. survival:
  - HPV+ 82%
  - HPV - 57%

Ang et al. NEJM 2010

- tumor HPV status is the single greatest predictor of survival for patients with local-regionally advanced OSCC.
- histologic ‘grade’ of SqCC is clinically irrelevant if HPV-related tumor
- relative to HPV-negative patients, HPV-positive patients have an ~ 60% reduction in risk of death
- corresponds to an absolute survival difference of ~ 30% @ 5-years

HPV testing – available methods for FNA specimens

- liquid-based assays
  - Hybrid capture 2
  - Corvista
  - Cobas HPV test
- HPV DNA
  - Southern blotting
  - in-situ hybridization
  - consensus PCR
  - type-specific PCR
  - real time PCR
- HPV RNA
  - reverse transcriptase PCR
  - HPV RNA ISH (RNAscope®)
- HPV proteins
  - IHC for E6, E7
- surrogate markers
  - p16 IHC
  - pRB IHC
in tissue:
typical threshold for positive p16 result =
nuclear & cytoplasmic staining in ≥ 70%
malignant cells

what about cytology CBs?

- p16+ in 47/48 cases (98% concordance)
- collected in RPMI, fixed with cytoRich Red
- used RNAscope HPV kit
- p16+ in CB ranged from 15-100% even when staining was
diffuse in corresponding tissue section
- using threshold of 70% staining = high number FN results
- propose: cutoff of strong p16+ in ≥15% of tumor cells in CB
  = 98% concordance with tissue specimen
• 63 FNAs/60 pts. – all with p16+ on whole tissue sections
• 80% oropharyngeal primary
• using a 70% minimum p16+ threshold
  – sensitivity = 39%, NPV = 26%
  – recommendation: 70% cutoff should not be applied to cytology
• using a ≥ 10% minimum p16+ threshold
  – best correlation with hi-risk HPV CISH
  – best overall concordance rate with tissue p16 IHC

HPV Methodology
• no universal consensus on best method
  – RT-PCR for E6/E7 viral oncogene mRNA (gold std.)
    • requires fresh frozen tissue, technically cumbersome
  – IHC/ISH for HPV DNA
  – IHC for E6/E7
  – PCR for HPV DNA or HPV RNA
• differing sensitivity/specificity/cost
• guidelines from CAP expected

case 3
• 34 y/o man presents with a 1 cm. right neck nodule x 2 weeks.
• prior history of sinonasal tumor
Neck Masses that have ‘virtually identical FNA cytomorphology’

- metastatic small cell NEC
- metastatic olfactory neuroblastoma [ONB]
- metastatic Merkel cell carcinoma
- metastatic SNUC
- metastatic NUT midline carcinoma

another ‘small cell’ case

- 43-year old woman presented with a R cheek nodule
- size unknown
- no other history
Diagnosis = MALIGNANT BASALOID NEOPLASM ??
Diagnosis

PILOMATRIXOMA

'ghost' cells
another ‘small cell tumor’ case

• 21 y/o woman presents with a 2 cm. R cheek mass x 1 month, and

• a 3 cm. R neck mass x 1 week.
IHC cell-block

**positive**
- desmin
- myogenin
- CD56
- FKHR t(2;13) by FISH

**negative**
- S-100
- melan-A
- HMB-45
- cytokeratin AE1/3
- myoglobin
- TTF-1
- calcitonin
- synaptophysin

Dx = alveolar RMS

RMS – Adult Head & Neck

<table>
<thead>
<tr>
<th>Reference</th>
<th># cases</th>
<th>Age (yr.)</th>
<th>Site</th>
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<tr>
<td>Montone et al. 2009</td>
<td>13</td>
<td>18-86</td>
<td>12/13 parameningeal</td>
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<tr>
<td></td>
<td></td>
<td>x = 39</td>
<td></td>
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<tr>
<td>- 3 ERMS</td>
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</tr>
<tr>
<td>- 9 ARMS</td>
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<td></td>
<td></td>
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<tr>
<td>- 1 unclassified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yasuda et al. 2000</td>
<td>7</td>
<td>49-76</td>
<td>5/7 parameningeal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>x = 62</td>
<td></td>
</tr>
<tr>
<td>- all ARMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSU study</td>
<td>15</td>
<td>19-80</td>
<td>13/15 parameningeal</td>
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<tr>
<td></td>
<td></td>
<td>x = 47</td>
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</tr>
<tr>
<td>- all ARMS</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
COG. Morotti R et al. Am J Pathol 2006; 30:962 1,052 sarcomas

- 956 RMS
  - 508 embryonal
  - 416 alveolar
  - 32 NOS
- 31 undifferentiated sarcoma
- 65 non-RMS tumors
  - Ewing, pPNET, rhabdoid t., pleuropul. blastoma.
- myogenin expression > MyoD 1

<table>
<thead>
<tr>
<th></th>
<th>sens (%)</th>
<th>spec (%)</th>
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<tr>
<td>myogenin</td>
<td>97</td>
<td>90</td>
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<tr>
<td>MyoD 1</td>
<td>97</td>
<td>91</td>
</tr>
<tr>
<td>desmin</td>
<td>99</td>
<td>71</td>
</tr>
<tr>
<td>actin</td>
<td>70</td>
<td>-</td>
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</table>

• conclusion: immunostains against intranuclear myogenic transcription factors are the best available for confirming the dx of RMS

Large Polygonal Cell Lesions (cytoplasmic-rich)
**D DX**

- granular cell tumor
- rhabdomyoma, adult type
- ASPS
- paraganglioma
- melanoma
- lymphoepithelioma
- metastatic renal cell CA

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**Granular Cell Tumor**

- H/N sites: **tongue**, soft tissue, oral cavity, larynx
  - 10% have multiple primary tumors
- 99% benign
  - ~5% local recurrence
- F:M; 2:1
- 4th – 5th decade

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**Granular Cell Tumor, H&N**

- cytology
  - moderately cellular smears
  - polygonal/epithelioid cells
  - loose syncytia & single forms
  - cytoplasm
    - fine to coarse cytoplasmic granularity
  - spherical to oval nuclei
  - nucleoli may be obvious
  - bare nuclei common
granular cell tumor

granular cell tumor

granular cell tumor
Granular Cell Tumor, H&N

- positive
  - ± PASD
  - S-100
  - SOX10
  - ± NSE
  - calretinin
  - ± inhibin
  - CD68
- negative
  - CK
  - actin/desmin
  - HMB-45

Rhabdomyoma

- Cardiac

- Extra-Cardiac
  - Adult
  - Fetal
  - Genital

Adult Rhabdomyoma

- H/N sites
  - larynx, floor of mouth, oropharynx, orbit, soft tissue of the neck
- wide age range, most > 50 years
- M > F, 4:1
- slow-growing
- ~16% local recurrence
Paraganglioma

- 4th - 5th decade
- chief/sustentacular cells
- 70% of all extra-adrenal PGs in H/N
- malignant: ~ 3% cases
- IHC:
  - synaptophysin
  - chromogranin
  - S-100+
  - pan-keratin neg.

Paraganglioma

- cytopathology
  - bloody, bloody, bloody
  - both clusters, singly dispersed
  - anisonucleosis, stripped nuclei
  - finely granular cytoplasm
  - absence of lymphoglandular bodies
case 4

- 76 y/o ♂ presents with a 2.5 cm. left posterior neck mass x 2 months
- no other lesions
- no pertinent past medical history
Dx = Nasopharyngeal Carcinoma, Non-Keratinizing, Undifferentiated (lymphoepithelioma), metastatic

N-P Carcinoma

2017 WHO classification
- Keratinizing SqCCA
- Non-Keratinizing SqCCA
  - differentiated type
  - undifferentiated type
- Basaloid SqCCA
- Papillary Adenocarcinoma

- commonly presents as an asymptomatic neck mass
- posterior cervical triangle
- EBV+

LELCs – Head & Neck

- Sinonasal
- Nasopharynx
- Hypopharynx/Larynx
- Salivary Gland
- Skin
- Oropharynx
Cystic Lesions

DDx

- branchial cleft cyst
- chronic sialadenitis
- salivary duct cyst
- cystadenoma
- lymphoepithelial cyst
- thyroglossal duct cyst
- met cystic SqCCA
- l-g mucoEp CA
- cystadenocarcinoma
- cystic Warthin T.
- met cystic PTC

Cystic nodules of the lateral neck are challenging. FN rates range from 38-63%. Layfield et al. Diag Cytopathol 2016; 44:561.

Branchial Cleft Cyst

- derived from remnants of 2nd branchial arch apparatus
- along anterior border of SCM
- children
- 75%, 20-40 yrs.
- ddx metastatic SqCC
• 2nd BCC
  – from Thompson & Wenig, Diagnostic Pathology: Head & Neck

branchial cleft cyst

branchial cleft cyst
branchial cleft cyst

acute inflammation, histiocytes interpreted as SCC
branchial cleft cyst. 53 y/o ♀ called suspicious for CA

branchial cleft cysts may show focal p16 + staining

•  benign lymphoepithelial cysts – tissue
  – p16 staining in 16/37 (43%).

•  benign lymphoepithelial cysts – aspirates
  – p16 staining in 5/12 (42%)
p16 + Neoplasms

outside H/N
- SqCCA
- adenoCA, multiple sites
- ductal breast CA
- papillary thyroid CA
- cellular schwannoma
- NUT midline CA
- Ewing sarcoma
- some melanomas

Head & Neck
- SqCCA
- adenoid cystic CA
- nasopharyngeal CA
- adenoCA, NOS
- small cell NEC
- large cell NEC
- mucoEp CA
- CA ex PA

• 67 y/o ♂
• 3 cm. cystic swelling
  R mid neck x 6 months
• cytospin slide
• Pap stain

• 67 y/o ♂
• 3 cm. cystic swelling
  R mid neck x 6 months
• cytospin slide
• Pap stain
metastatic HPV-related non-ker. SqCCA

cystic neck mass. 38 y/o ♀
keratinizing SqCCA

cystic SqCCA

neck mass, 35 y/o ♀

keratinizing SqCCA

• 33 cases; all SP confirmed
  – 21 SqCCA
  – 12 BC Cyst
  – 19 morphologic features assessed

• best discriminators
  – small cell clusters
  – high N/C ratio
  – irregular nuclear membranes

Fig. 1. Decision tree for diagnosis of cystic neck lesion. Prob diagnosis (the probability of malignancy).

BCC – Take Home Messages

• don’t make a Dx of branchial CC without considering the possibility of metastatic SqCCA regardless of patient age or the clinician’s clinical diagnosis

• look carefully for cytologic atypia

• it’s always risky to make an unqualified FNA Dx from sparsely cellular specimens


Spindle Cell Lesions

Schwannoma
Nodular Fasciitis
Schwannoma

- 20-50 yrs.
- head & neck
  - cranial nerves (VII N.)
  - lateral neck
  - tongue

- histopathology:
  - Antoni A
  - Antoni B
  - Verocay bodies
  - encapsulated, cystic change
  - vasculature hyalinization
  - S100, SOX10 +

fibrillar syncytial clusters
• schwannoma FNA = 58 v. non-schwannoma FNA = 98

• highlighted 5 morphologic features:
  • high number of cell clusters
  • few/no single cells
  • fibrillary stroma
  • pointed tip nuclei
  • anisonucleosis

• if all 5 present
  • sensitivity: 22%
  • specificity: 97%
  • PPV: 81%
  • NPV: 68%

Cancer. 2015; 123: 171.
Schwannoma \([n=39]\) *

- benign fibrous/Sp C lesion \([3]\) †
- salivary gland neoplasm \([1]\) †
- susp. spindle cell sarcoma \([1]\) †

* all primary histologically proven

unpublished data
Schwannoma [n=39]*

- actual FNA Dx:
  - schwannoma [33]
  - susp. schwannoma [1]*

- 85% * * *

*66% IHC

- benign fibrous/Sp C lesion [3]†
- salivary gland neoplasm [1]†
- susp. spindle cell sarcoma [1]†

Nodular Fasciitis

- 20-50 yrs.
- common, subQ
  - rapid growth
  - self-limited
  - reactive process
- solitary
  - well-circumscribed
  - fibroblasts/myofibroblasts
  - SMA, MSA, calponin
- < 2% recur
- USP6 - FISH

nodular fasciitis

- 52 cases
  - 46 NF, 3 PF, 3 PM
- 88% spontaneous resolution
- 12% tissue biopsy
- accuracy:
  - 88%; 12% called FH, myxoma
- cytopathology
  - hypercellular
  - fibroblast-like
  - nuclei: oval, round, tapered
  - ganglion-like cells
  - multinucleated GC (8 cases)

myxoid change in NF

nodular fasciitis
Topics

• Non-lymphoid Small Cell (cytoplasmic-poor)
• Non-lymphoid Large Cell (cytoplasmic-rich)
• Cystic
• Spindle cell

Nodular Fasciitis: A Frequent Diagnostic Pitfall on Fine-Needle Aspiration

Derek B. Allison, MD,1 Paul E. Wakefly Jr, MD,1 Momin T. Siddiqui, MD, FACP,2 and Syed Z. Ali, MD, FACP3

[Image: University Hall, OSU main campus]
fun case

• 45 year old HIV-positive man
• 5 cm. slightly raised red-black plaque
  skin of his face x 3 months
• FNA incorrectly interpreted as ‘non-diagnostic’
• skin biopsy was performed.
Leishmaniasis

<table>
<thead>
<tr>
<th></th>
<th>Cutaneous</th>
<th>Visceral (kala azar)</th>
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<tbody>
<tr>
<td><strong>species</strong></td>
<td><em>L. tropica</em>, <em>L. mexicana</em>, <em>L. braziliensis</em></td>
<td><em>L. donovani</em>, <em>L. infantum</em>, <em>L. chagasi</em></td>
</tr>
<tr>
<td><strong>location</strong></td>
<td>Africa, Middle East, southern Europe, Latin America</td>
<td>Asia, Middle East, Africa, Mediterranean basin</td>
</tr>
<tr>
<td><strong>clinical</strong></td>
<td>cutaneous ulcer, or papules, diffuse form, mucocutaneous form</td>
<td>intermittent fever, marked hepatosplenomegaly, pancytopenia, skin pigmentation in India</td>
</tr>
</tbody>
</table>

**Brown-Hopps Gram stain**
female sandfly
*Phlebotomus*, Eastern Hemisphere
*Lutzomyia*, Western Hemisphere

Cutaneous Leishmaniasis
flagellated leptomonad

Leishmanial/amastigote form
reservoir hosts

Leishmania
Histoplasma
Leishmaniasis vs. Histoplasmosis

<table>
<thead>
<tr>
<th></th>
<th>Leishmaniasis</th>
<th>Histoplasmosis</th>
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<td>GMS, PAS</td>
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<td>+</td>
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<tr>
<td>Brown-Hopps Gram</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Size</td>
<td>1.5 – 3 μ</td>
<td>2 – 4 μ</td>
</tr>
<tr>
<td>Clear zone</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Kinetoplast</td>
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