Diagnostic Cytology Seminar

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There is no disclosure necessary

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There is no disclosure necessary

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There is no disclosure necessary

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ASC Diagnostic Cytology Seminar

November, 2012
Las Vegas, NV

P.E. Wakely, Jr., M.D.
Wexner Medical Center @
Ohio State University
Columbus, OH
U.S.A.

• 2:00 – 3:30 DCS session
• 3:30 – 4:00 Break
• 4:00 – 5:00 DCS session
My Role In This DCS

• charge to each panelist
  – want the audience to see your thought processes
  – what made you think of a certain set of entities
  – how did you narrow this limited info down to your final interpretation or set of interpretations

• end result → help YOU the audience

8 Cases

- Soft Tissue
- Cervix
- Body Cavity Fluid
- Thyroid
- Salivary Gland
- Skin

CASE 1
Gladwyn Leiman, MBBCh, FIAC, FRCPath

- Professor of Pathology
- Director of Cytopathology
- University of Vermont School of Medicine
  Burlington, VT

cases 1 and 5

ASC Slide Seminar
Las Vegas

November 2012
Gladwyn Leiman
Case 1. Dr. Leiman. A 10 month old female developed a 1.5 cm. mass on her left foot. There is no relevant medical history. FNA biopsy was performed.
Case 1
INFANTILE INCLUSION BODY FIBROMATOSIS

Alternate/Historical Names
- Infantile digital fibromatosis
- Recurring digital fibroma
- Reye tumor

Clinical Criteria

- Under 1 year of age, or even congenital
- Most on lateral digits of hands and feet
- Size usually 1-2cm
- Involve dermis and subcutis
- Poorly circumscribed
- May be multifocal, metachronous
Histopathology

- Cellular lesion with bundles of spindle cells
  - Vesicular nuclei
  - Fibrotic stroma

- Perinuclear round eosinophilic inclusions
  - Vary from rare to frequent
  - Approximately size of erythrocytes (3-15 microns)
  - Red on trichrome stain
  - Blue on Giemsa stain

- Mitotic figures may be present but not atypical

Differential diagnosis

- Infantile fibromatosis
- Fibrous hamartoma of infancy
- Fibroma of tendon sheath
- Infantile fibrosarcoma
- Plantar fibromatosis
- Nodular fasciitis
- Myofibroma
- Neurofibroma
- Leiomyoma

Differential Diagnosis

Fibrous Hamartoma of Infancy

- Not reported in digits, hands or feet
- Triphasic - spindle cell fibrous areas
  - adipose tissue
  - clusters of immature mesenchyme
- No inclusions
Differential Diagnosis

Infantile Fibromatosis
- Rare in hand and foot
- Usually >2 cm
- Involves skeletal muscle
- Muscle not involved
- No inclusions

Immunohistology

<table>
<thead>
<tr>
<th>Spindle cells</th>
<th>Inclusion bodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth muscle actin 100%</td>
<td>SMA +, may require special fixation or pretreatment</td>
</tr>
<tr>
<td>Calponin 100%</td>
<td></td>
</tr>
<tr>
<td>CD99 100%</td>
<td></td>
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<tr>
<td>Desmin 100%</td>
<td></td>
</tr>
<tr>
<td>CD117 75%</td>
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<tr>
<td>CD34 9%</td>
<td></td>
</tr>
<tr>
<td>Keratin 1%</td>
<td></td>
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<tr>
<td>β-catenin 0%</td>
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</table>

Follow up

- Frequent spontaneous regression
- Larger ones may require excision or even digital amputation
- Recurrences occur, non destructive
- Never metastasizes
How did I do?

How did YOU do? – The FNA?

nodule resected
Case 1 - ASC Website Diagnoses

- Sarcoma
- Spindle Cell Neoplasm
- Fibromatosis
case 1 - Panelist’s Diagnoses

- inclusion body fibromatosis x 2
- nodular fasciitis

Case 1 - DIAGNOSIS

INCLUSION BODY FIBROMATOSIS
(RECURRENT DIGITAL FIBROMA)

R.D.K. Reye 1921-1977

- Fibrous Hamartoma of Infancy 1956
  - Reyeoma 1
- Inclusion Body Fibromatosis (recurrent digital fibroma)
  - Reyeoma 2 1965
- Reye syndrome
  - encephalopathy
  - visceral steatosis
Inclusion Body Fibromatosis

- 1st year of life
- non-tender dome-shaped swelling
  - dorsum of fingers or toes
- may recur / may spontaneously regress
- uniform spindle cells/ intra-cytoplasmic inclusions (actin)
- IHC: actin, desmin, calponin +
- Rx: local excision

Lesions with intra-cytoplasmic actin positive inclusions

Inclusion Body Fibromatosis

Intranodal Myofibroblastoma

Leiomyoma

Aspiration Biopsy Cytology of Intranodal Myofibroblastoma: Case Report With Immunocytochemical Analysis

Angelo P. Di Tosi, M.D., Dullio Della Libera, M.D., and Lucia Bittesini, M.D.

Infantile Fibrosarcoma

- < 2 yrs. of age; rare on toes or fingers
- very large, often > 5 cm.
- highly cellular
- lack intracytoplasmic inclusions
- favorable prognosis
CASE 2
Case 2

- History: 52 year old woman presents with intermittent vaginal bleeding. A polyp was seen on the anterior lip of the cervix. She has no relevant medical history. A liquid based Pap smear was obtained.
Our training tells us…

- 50+ age group introduces many differentials, first the horses:
  - Evidence of a polyp grossly could possibly show reactive reparative change which could be florid.
  - Benign atrophy with mild atypia should be considered.
  - Did she have an IUD someone forgot about?
  - Between the ages of 45-55 squamous cell carcinoma is the most common malignancy of the uterine cervix.
  - Endocervical Adenocarcinoma of the cervix represents approx. 25% of cervical cancers. Age groups vary.
  - Endometrial adenocarcinoma most commonly found in women in their late 50s. (maybe not so much anymore)

Differentials continued…

- Non-epithelial malignant tumors: the zebras!
  - Most common would be metastasis from ovarian or fallopian neoplasms.
  - Tumors invading locally: colon, or rectal, bladder and urethral carcinomas would follow in incidence.
  - Finally tumors from distant metastasis.
Initial Observations

- History was intermittent bleeding—observed no blood in the background.
- Smear background pattern was that of a post-menopausal woman. Appeared to be scattered atrophic cells.
- Low-level observation leads us to honing in on single cells present on slide.
- Let's take a tour of the single cells that can be found in a pap test.
Differentials to consider

- Reparative change
  - Polyps, benign proliferative reactions
  - However, repair typically occurs in flat, monolayer sheets. Single cells are not usually identified.
- Gynecologic lesions
  - ASC-US
  - ASC-H
  - Single cells from a HSIL or CA
- Extrauterine malignancies
  - Metastatic serous CA, Distant metastasis, Non-epithelial malignancies

Considering parabasal atrophy.
- Usually identified as flat sheets of immature squamous cells arranged in a paving stone like fashion.
- Parabasal cells may show mild variation in nuclear size.
- Contours should only be slightly irregular
- Should only be slightly hyperchromatic.

Single cells from ASC-H lesion.
- Cells have high N/C ratio
- Atypical nuclear borders
- Three dimensional quality to nucleus with prominent folding
- Cytoplasm is primitive
- Features are shy of HSIL
Changes associate with IUD
• Glandular cells present singly or in small clusters amid a clean background.
• Large vacuoles can displace the nucleus causing a signet ring appearance.
• Cells have increased nuclear size, and high N/C ratio, some cells can show a prominent nucleolus.

Single cell from unknown case.
• Single cell has squamoid characteristics, cytoplasm abundant and dense.
• Nuclear shape is round with nucleus more centrally located.
• Chromatin pattern is irregularly finely granular.

Single cells from known squamous cell carcinoma.
• Differential stain shows keratinization.
• Single cells have much less abundant cytoplasm with high N/C ratio.
• Chromatin is coarsely granular with margination.
Single cell from unknown case.
- Cell size is larger
- Cytoplasm is more dense, demonstrate two-tones.
- Nucleus is eccentrically located
- Nucleus is hyperchromatic with chromatin irregularly distributed
- Prominent nucleolus is easily discernible.

Single cell from known metastatic lobular carcinoma.
- Also eccentrically placed nucleus
- More irregular nuclear shape
- Chromatin pattern; irregularly finely granular.
- Multiple smaller nucleoli
- Cytoplasm much more delicate.

Single cell from unknown case.
- Comparing to cells in background this is a large cell!
- Nucleus is eccentrically located, but N/C ratio is about 30%.
- Hyperchromasia is noted, but no chromatin clearing.

Single cell from known metastatic papillary serous carcinoma.
- Still eccentrically located
- N/C ratio is about 80% of cell
- Chromatin clearing is evident as well as chromatin margination.
- Conspicuous nucleoli are centrally located.

Cells from unknown case demonstrate single cells with intranuclear cytoplasmic inclusions.

Cells from a patient known to have brachytherapy type radiation also can have nuclear inclusions.
- Note sheet-like arrangement with cobblestone appearance of cells.
Aggregate from Unknown case
- Loosely cohesive; cytoplasm doesn’t appear shared between cells.
- Nucleus angulated; chromatin not discernible.
- Pigment is prevalent with greenish brown color; though cytoplasmic also overlies nucleus.

Aggregate from radiated cervical CA.
- Cytoplasm is delicate and shared between cells.
- Nucleus is angulated with hyperchromasia.
- Pigment isolated to cytoplasm and greenish color is consistent with hemosiderin breakdown.

Other observations of pigment

Gestalt Diagnosis
- Primary cervical melanoma is a rare neoplasm of the female genital tract, with less than 50 cases reported in literature. Gupta R, Singh S, Mandal AK. Primary malignant melanoma of cervix - a case report. Indian J Cancer 2005;42:201-4.
  - Cytomorphology consists of isolated cells, can be epithelioid or spindled.
  - Round to oval nuclei with prominent eosinophilic nucleus or intranuclear inclusions are commonly observed.
  - If you are lucky, you get pigment...

WE GOT LUCKY!
My Diagnosis

- Malignant melanoma.
  - Use immunostains to confirm HMB-45, MITF, Melan-A or S100.
IHC, case #2

- positive
  - S-100
  - Melan-A
  - HMB-45

- negative
  - cytokeratin AE1/3

Case 2 - ASC Website Diagnoses

- Melanoma
- AdenoCA
- NILM/Histiocytes
case 2 - Panelist’s Diagnoses

- Granulocytic Sarcoma
- Malignant Melanoma
- Malignant – favor Melanoma

Case 2 - DIAGNOSIS

METASTATIC MALIGNANT MELANOMA, UTERINE CERVIX


Melanoma, Cervix

- vulva, vagina (primary); cervix (metastatic)
- exophytic or ulcerated
- bleeding
- poor prognosis
- cytomorphology
  - primarily single cell pattern, ± diathesis
  - eccentric nuclear placement, ± INI
  - ± macronucleoli, most pigmented
THE CELL
IN HEALTH AND DISEASE

An Evaluation of Cellular Morphologic Expression of
Biologic Behavior

By John K. Frost
Associate Professor of Pathology, Johns Hopkins University School of Medicine;
Pathologist and Head of Department of Cytopathology,
The Johns Hopkins Hospital, Baltimore, Maryland

With 81 figures, 2 diagrams and 15 charts
- cells are usually single
- “extremely good nuclear malignant criteria”
- size variation of pigment granules is > what one finds in hemosiderin, bile, carbon, lipofuscin, & other pigments
- “melanin does not continue to gleam as one lowers the condenser”

**gleam**

df: to shine with or as if with subdued steady light or moderate brightness
in melanoma, abnormalities of squamous cells may be observed . . . site of origin has not been determined “
Clinical History

A 62 y/o man presented with a left thigh mass of unknown size and duration. He has no relevant medical history. FNA biopsy was performed.
My Initial Thoughts…

- Why is Paul Wakely sending me something that doesn't look like a sarcoma?
- ...maybe it is a sarcoma…
- Small round blue cell sarcoma with cytoplasmic vacuoles in 62 y/o?
  - Round cell liposarcoma?

Liposarcoma

The higher the grade of liposarcoma, fewer cytoplasmic vacuoles were present.

Other sarcomas?

- Wrong age
- Wrong clinical presentation

…maybe it’s not a sarcoma.

What else (without using Dr Wakely as a clue)?

- Benign: Reactive/inflammatory
- Myeloid proliferations
  - Extramedullary Hematopoiesis
  - Myeloid Sarcoma
- Carcinoma, signet ring type
- Lymphoid neoplasm
- Malignant Melanoma

Not Reactive/Inflammatory

- Scattered small lymphoid cells present
- No neutrophils
- Histiocytes scant
- Cellular monotonous population argues for neoplasm

?Extramedullary Hematopoiesis

Case 3

NO- Not EMH
Myeloid Sarcoma

- Morphologic features
  - Cells will show a spectrum of change within the myeloid lineage.
  - Eosinophilic myelocytes
  - Nuclei can show folding, irregularity
  - Chromatin is more open or finely granular

Myeloid Sarcoma

Case 3

Not Myeloid Sarcoma…

Metastatic Melanoma

Cells are much smaller than typical Melanoma
Would expect more abundant cytoplasm (plasmacytoid look)
More prominent nucleoli in typical Melanoma
Metastatic Carcinoma?

- Age is good
- Most common carcinomas presenting as soft tissue masses
  - Renal cell carcinoma
  - Pulmonary carcinoma
  (signet ring forms uncommon)
- GI, Prostate, Bladder can all have signet ring differentiation (uncommon presentation)
- Small cell carcinoma

Metastatic Signet Ring Carcinoma

Merkel Cell Carcinoma
Small Cell Carcinoma— with signet rings?

Small cell carcinoma with cytoplasmic vacuoles

- More angular nuclei
- Chromatin a bit more dense
- Nuclear molding apparent— even in pleural fluid specimen

Lymphoma

Large Cell Lymphoma

A match?

Hematolymphoid

- Lymphoma: Morphologic Features
  - Large vs Medium vs Small (relative to histiocyte nucleus) Case 3- “large vs medium”
  - B cell vs T cell (monotonous vs multiple cell types, pleomorphic) Case 3- “B cell”
  - Follicular vs Diffuse (hard to tell on aspirate)
  - Cleaved vs Noncleaved nuclei
    - Noncleaved (typical of diffuse large B cell lymphomas) - round, smooth membrane, chromatin relatively fine, multiple nucleoli (peripheral), basophilic cytoplasm *Case 3
    - Cleaved (typical of follicular lymphomas) - ovoid, deep nuclear folds, chromatin more coarse than noncleaved, 1-2 nucleoli

Extranodal lymphomas- large cell lymphoma most common
But what about a lymphoma with cytoplasmic vacuoles?

Courtesy of Dr Bill Macon

It Could be….

Lymphoma with Signet Ring Features

- Rare morphologic feature (variant) of Non-Hodgkin lymphoma (majority are B cell)
  - Most commonly in follicular lymphomas
  - Diffuse large B cell lymphoma
  - MALT lymphoma
  - Small lymphocytic lymphoma
  - T cell lymphoma
- Can involve nodal tissue or extranodal location including cutaneous structures
- Importance is to recognize lymphoid etiology so that proper subclassification and treatment can be determined.
<table>
<thead>
<tr>
<th><strong>Small cell carcinoma with signet ring features</strong></th>
<th><strong>VS</strong></th>
<th><strong>Large cell lymphoma with signet ring features?</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Without Immunohistochemical stains…</td>
<td></td>
<td></td>
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<tr>
<td>• Classic Morphologic Carcinoma vs Lymphoma Differential</td>
<td></td>
<td></td>
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<tr>
<td>– Lymphoglandular bodies</td>
<td></td>
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<tr>
<td>– Chromatin</td>
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<tr>
<td>– Dyscohesion vs nuclear molding</td>
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**Case 3**

**Lymphoglandular Bodies**

**Chromatin- Uniformly dispersed**

**Nucleoli- 1 or more, not prominent**

**Case 3**

No Nuclear Molding or cohesion
My Diagnosis:
Large Cell Lymphoma with Signet Ring Features, likely B-cell phenotype

Case 3 - ASC Website Diagnoses
- Lymphoma
- Ewing Sarcoma/PNET
- Liposarcoma

Case 3 - Panelist’s Diagnoses
- MSRCT, favor Ewing Sarcoma
- Signet ring neoplasm: carcinoma vs. lymphoma (I know it is rare)
- Synovial sarcoma
lesion excised
Case 3 - DIAGNOSIS

FOLLICULAR LYMPHOMA, SIGNET-RING CELL VARIANT

Signet ring cell lymphoma
A rare morphologic and functional expression of nodular follicular lymphoma
The wearing of signet rings (from Latin "signum" meaning sign) goes back to ancient Egypt.

Signet Ring Cell Lymphoma

- rather rare; not an entity per se
- morphologic variant of FL, but also in other B-and T-cell lymphomas
- vacuole:
  - Ig filled or empty
  - mucin negative
- immunophenotype, behavior
- importance lies in confusion with carcinoma

Lesions Having Signet Ring Cells

- Adenocarcinoma (GI, breast, prostate)
- Lymphoma (large cell, FL, MALT)
- Melanoma
- Pseudomembranous colitis
- Liposarcoma
- GIST
- Mesothelioma
- Sinus Histiocytosis
- Ovarian stromal tumor
- Decidualized endometrial stroma
Lesions Having Signet Ring Cells

- Adenocarcinoma (GI, breast, prostate)
- Lymphoma (large cell, FL, MALT)
- Melanoma
- Pseudomembranous colitis
- Liposarcoma
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- Mesothelioma
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- Ovarian stromal tumor
- Decidualized endometrial stroma
Joseph Jakowski, M.D.

- Asst. Professor of Pathology
- Asst. Director of Cytopathology
- Director of US-Guided FNA Service
- MCV-VCU Health System
  - Richmond, VA

cases 4 and 8
A 49 year old man presented with shortness of breath, ascites, and a right pleural effusion.

Pleural fluid specimen: Romanowsky and Pap stained Cytospin Preparations
CASE 4

History analysis

49 yo man shortness of breath

PMH? Immune status? Imaging?

Ascites

Transudate

Benign (inc. Infectious)

Pleural effusion

Exudate

Malignant:
Carcinoma (~75%)
Hematopoietic (~10-15%)

Romanowsky stained Cytospin

Romanowsky stained Cytospin
**CASE 4**

- Plasmacytoid
- Coarse chromatin
- Perinuclear hof?
- Peripheral basophilia

Pap stained stained Cytospin

Romanowsky stained Cytospin
CASE 4 Differential Diagnoses

✓ MALIGNANT Effusion

Carcinoma  ✓ Hematopoietic

Mesothelioma  ○ OTHER?

Sarcoma
MeAnoma

CASE 4 Differential Diagnoses

✓ Lymphoma:
Pyothorax-associated lymphoma
Burkitt lymphoma
ALCL
Anaplastic myeloma
Primary effusion
DLBCL

Large Cell
Plasmacytoid features
No Lymphadenopathy/Body cavity
Primary Effusion Lymphoma

Case 4 - ASC Website Diagnoses

- L-P Disorder/PEL
- Mesothelioma
- Myeloma

Case 4 - Panelist’s Diagnoses

- ALCL vs. PEL
- Richter Syndrome - transformation to high grade hematolymphoid malignancy
- T-cell rich DLBL?
Case 4 - DIAGNOSIS
PRIMARY EFFUSION LYMPHOMA (PEL)

PRIMARY EFFUSION LYMPHOMA
- rare, immunosuppressed
- prototype: HIV+ young man, some HIV -
- largely restricted to body cavities
  - pleural, pericardial, peritoneal
  - rarely extra-cavitary “solid”

PRIMARY EFFUSION LYMPHOMA

- rare, immunosuppressed
- prototype: HIV+ young man, some HIV-
- largely restricted to body cavities
  - pleural, pericardial, peritoneal
    - rarely extra-cavitary
- IB/ PB/ anaplastic lymphoma morphology
- KS-HHV-8 (almost universal)

PRIMARY EFFUSION LYMPHOMA (PEL)

- positive
  - HHV-8, CD45
  - EBER (80%)
  - activation Ag’s
  - CD30, EMA, CD38, CD138
- negative
  - B-cell: CD 20, 19, 79a, PAX-5, slg
  - T-cell: CD 2, 3, 5
    (some aberrant T-cell staining)

Plasmablastic Phenotype

- PEL
  - Anaplastic/Plasmablastic Myeloma
  - Plasmablastic Lymphoma
  - Alk+ Large B-Cell Lymphoma
  - Large B-Cell Lymphoma Arising in HHV-8
    Multicentric Castleman D.
  - DLBL with partial plasmablastic differentiation
Case 5. Dr. Leiman.

A 66 year old man presents with right cervical adenopathy. He had a total thyroidectomy performed 10 years earlier. He also has a floor of mouth ulcer. FNA biopsy was performed on the neck mass.
Talk Cytology

- Background adipose, muscle and lymphoid cells
- No mucus, no mesenchymal stroma, no blood
- Cellular +++ Single cells, sheets, “glomeruloid”
- Numerous vessel-based cell aggregates
- Multiphasic-looking malignant cell population
  - Tall columnar-shaped cells with blebs
  - Spindled, dense cytoplasm
  - Hypervacuolated cells, prominent inclusions
- Chromatin dark, no macronucleoli

Differential diagnosis

**NOT** - Lymphoma
  - Melanoma
**COULD BE** - Carcinoma
  - Germ cell tumor
  - Sarcoma

REAL WORLD DIAGNOSIS

- Thyroid is likely a red herring – unless RT
- The floor of mouth is the primary site
- Likely we are looking at carcinoma
- It has dual differentiation
- I think it is a **MUCOEPIDERMOID CA**
- If metastatic, **UROTHELIAL CARCINOMA**
Sarcomas of the oral cavity

- Vascular sarcomas
- Liposarcomas
- Fibrohistiocytic sarcomas
- Neural sarcomas
- Synovial sarcomas
- Alveolar soft part sarcomas
- Clear cell sarcomas
- Dendritic cell sarcomas
- Leiomyosarcoma/Rhabdomyosarcoma
- Osteo and chondrosarcomas

This case: One likely sarcoma

- **KAPOSI's SARCOMA:**
  - Occurs in mucous membranes
  - Vascular proliferation, red cells admixed
  - Fusiform spindle cells
  - Cytoplasmic vacuoles with hyaline droplets
  - Fine chromatin and inconspicuous nucleoli

(Where's the blood? Such rounded vacuolization?)
This case: Another possible sarcoma

EPITHELIOID HEMANGIOENDOTHELIOMA
- Intermediate malignant potential
- Has been reported in oral cavity but rare
- Single and grouped cells, variable
- Epithelioid cells with abundant vacuolated cytoplasm containing red cell forms
- Some groups glandular, sheet or rosette-like formations

This case: Another possible sarcoma

EPITHELIOID ANGIOSARCOMA
- May occur in head and neck
- High grade tumor, poor prognosis
- Can metastasize to lymph nodes
- Demonstrate pleomorphism, vacuolation
- Epithelial and vaso-formative features

(Where are the large nucleoli?)
REAL WORLD ACTION

• Review the slides of the floor of mouth tumor – the answer will be there!

• Otherwise do appropriate immunochemistry – epithelial, vascular, other.

Case 5 - ASC Website Diagnoses

- MucoEp CA
- AdenoCA, NOS
- FTC
- Chordoma
### case 5 - Panelist’s Diagnoses

- Mucinous/Signet ring cell variant of Papillary Thyroid Carcinoma
- High-Grade MucoEpidermoid Carcinoma
- Malignant; DDx – High-Grade MucoEp CA, ATC, and less likely, Sarcoma with epithelioid features

### original thyroid neoplasm
after FNA → neck dissection
case 5 - stains positive

- mucicarmine
- PAS
- PASD
- Alcian blue
- CK AE1/3
- thyroglobulin

mucicarmine

Alcian blue
Case 5 - DIAGNOSIS
METASTATIC MUCINOUS PAPILLARY THYROID CARCINOMA TO LYMPH NODE

Case 5 – Differential Dx
• malignant mucin-producing thyroid neoplasms

MUCIN PRODUCTION IN METASTATIC CARCINOMAS
EUGENE A. FOSTER, M.D., AND ALLAN JAY LEVY, M.D.
Cancer 16; 506-509, 1963

-review of ≈ 200,00 surgical specimens

“the thyroid is the only site studied that can be ruled out with great assurance when one is dealing with a mucicarmine-positive metastasis”
WHO: Primary Mucinous CA, Thyroid

- exceedingly rare, < 5 cases
- histopathology that of so-called "colloid" CA
  - bland cells
  - "pools" of mucin

MucoEp CA, Thyroid

- rare, < 0.5% thyroid malignancies
- histopathology similar to salivary gland l-g variant
- up to 60% mets to lymph nodes
- foci of PTC in up to 50% of cases
  - ? metaplastic variant of PTC
Mucin Production in Medullary Carcinoma of the Thyroid

• 36 cases of MTC; mucin in 42%
• 16%: mucin in both thyroid and lymph node metastases
• “as mucin may be present in nearly half of MTC, these lesions should be included in the ddx of tumors metastatic to cervical lymph nodes with mucicarminophilia.”

Metastatic Mucin-Producing CA to Nodes
– lung
– breast
– stomach

• 40 nodes containing metastatic PTC
• mucin in 58% of cases, often focal
take home messages

Yang GH

- a mucinous smear in a thyroid FNA does not necessarily indicate metastasis

- the presence of mucin in a cervical lymph node FNA does not exclude the thyroid as a possible primary source
Case 6

A 16 year old girl presents with a painless 2.2 cm. right neck mass of unknown duration. She is otherwise well with no relevant medical history. FNA biopsy was performed.
Physical exam

- Localize the region of the mass
  - Branchial cleft cyst would arise usually in the lateral part of the neck.
  - Thyroglossal duct cyst; usually midline in anterior neck.
  - Mucocele or retention cyst.
  - Thymic cysts present in the anterior mediastinum or between the angle of the mandible and the midline of the neck.

Physical exam considerations

- Cervical lymphadenitis from cat-scratch disease— inquiry about pets.
- Thyroid etiology.
- Salivary gland neoplasms.
- Hodgkin’s disease involving cervical nodes.
- Schwannoma

Ultrasonographic characteristics

- Cystic
- Involving soft tissue
- Involving nodes
- Solid
- Calcifications
  - Seen with pilomatrixoma, thyroid neoplasms
- Necrosis
Based on these first few images, I can exclude:

- Lymphadenopathy
- Hodgkin’s disease
- Thyroid carcinoma

Would like to examine further:
- Cystic lesions
- Salivary gland lesions
- Neurogenic lesions
**Branchial cleft cyst**

- Consists of superficial and intermediate squamous epithelium with evidence of inflammation

- The junky background fits, but no evidence of cholesterol crystals.
- You could see atypical keratinizing epithelium, BUT, you didn’t see spindle type cells in the background.

**Thyroglossal duct cyst?**

- Cytomorphology consists of varying consistencies of colloid, with macrophages, lymphocytes or neutrophils when infected.
- Epithelium present is mostly dilated columnar, metaplastic squamous. Thyroid epithelium is rarely identified.

**Hello?, This is too cellular!**

- And what about that mesenchymal stroma?
  - Nodular or Proliferative Fasciitis

- Pleomorphic adenoma
  - Most common neoplasm of the salivary gland
- Basaloid neoplasm (monomorphic adenoma)
- Schwannoma
  - Second most common, benign mesenchymal neoplasm behind lipoma.
Nodular Fasciitis
- Small, highly uniform appearing fibroblasts associated with a myxoid matrix.
- Small, but distinct nucleoli are present.
- Cytoplasm is indistinct and blends with surrounding cells.

Neurogenic Tumors
- Neurofibromatosis
- Schwannoma (Neurilemmoma)
- Paraganglioma
- Malignant peripheral nerve sheath tumor

Schwannoma
- Classical schwannoma consists of fishhook like spindle cells
- Stroma has distinctive fibrillar appearance that is delicate in nature
- Identify if Verocay bodies are present.
  - Kind of acellular areas surrounded by palisading nuclei
Malignant Peripheral Nerve Sheath Tumor
Cohesive tissue fragments, with relatively homogenous cells.
Intercellular cohesion changes with grade of malignancy
Can feature plump or elongate nuclei.
Are they myoepithelial in origin?

- Let's look at myoepithelial neoplasms
  - Myoepithelioma, epithelial-myoid epithelial carcinoma
  - Myoepithelioma (less than 1% of all salivary gland tumors)
    - Predominant cell type
    - Round type of cell with fine chromatin and absent nuclear atypia
    - Found as a single cell presentation with loose cohesion
    - Eccentrically located nucleus

Calponin Positivity in Myoepithelial Cells
But, But, But…
- Myoepitheliomas contain NO evidence of ductular formation!

Epithelial-Myoepithelial Carcinoma
- the presence of double-layered tubules consisting of duct epithelial cells (can be stained with pankeratin)
- surrounded by myoepithelial cells (identified with s100 and calponin)
- outer clear myoepithelial cell layers which are enveloped by basement membrane (Can use a PAS stain to demonstrate)
What type of epithelium is present?

Cylindromatous-type epithelium, making adenoid cystic like spaces.

Adenoid cystic carcinoma

- Consists of basaloid type cells surrounding hyaline stroma
  - Usually cribriform and cylinders encapsulating hyaline material

We definitely have architecture, but what about that stroma?!
Cue Thus Spake Zarathustra!

- My diagnosis: Pleomorphic Adenoma.
  - Contains an epithelial component
  - Contains a myoepithelial component
  - Contains a stromal component
  - Varying proportions of each component will be present.

Can have a WIDE variety of alterations.

- Ductal cells can be arranged in sheets, glands, trabeculae, or large branching fragments.

- Squamous metaplasia, oncocytic change, cystic degeneration, mucin production and sebaceous differentiation can be noted.
- Myoepithelial cells can be spindled or plasmacytoid.
- Can be associated intimately with chondroid matrix.
Case 6 - Panelist’s Diagnoses

- Pleomorphic Adenoma with Squamous differentiation
- Pleomorphic adenoma with Keratinization
- Benign Mixed Tumor with Squamous differentiation

surgical resection
Case 6 - DIAGNOSIS

PLEOMORPHIC ADENOMA WITH SQUAMOUS METAPLASIA

Pleomorphic Adenoma - Metaplasia

- Squamous
- Sebaceous
- Oncocytic
- Mucinous
- Goblet cell
- Clear cell
Squamous Lesions – salivary gland

- Squamous Cell Carcinoma
- Mucoepidermoid CA
- Squamous Metaplasia
  - Warthin Tumor
  - Pleomorphic Adenoma
  - Sebaceous Adenoma
  - Necrotizing Sialometaplasia
Warthin Tumor – Squamous Metaplasia

Branchial Cleft Cyst
Clinical History

A 45 y/o HIV-positive man presented with a 5 cm discolored lesion on the skin of his face. The 3 month-old lesion was slightly raised, red-black and plaque-like.
What am I thinking?

HIV positive patients - differential is broad
  – Opportunistic infection*
  – Neoplasm
HAART - Highly active antiretroviral therapy
  – Neoplasm*
    • Expanded spectrum
    • Cervical ca, Kaposi sarcoma, NHL, Hodgkin Lymphoma, Anal ca, Lung ca, Non-melanocytic skin ca, leiomyosarcoma
  – Opportunistic infection

Skin - “slightly raised, red-black plaque”…..Kaposi Sarcoma

Bloody background
Spindled cell neoplasm
Plump, moderate length elongate cells
Loosely cohesive
Not too cytologically atypical

Case 7
### Opportunistic Infection

Infectious organisms in skin/subcutaneous

- **Mycobacterial**: acid fast bacilli, tiny
- **Parasitic**
  - *Toxoplasma*: intracellular tachyzoites, 4-6um
  - *Leishmania*: intracellular amastigotes, 2-4um
- **Fungal**
  - *Histoplasma*: intracellular, 2-4um
  - *Blastomycosis*: extracellular, 5-20um

---

### Toxoplasma Gondii

- Tachyzoites: Crescent shaped organisms with blue cytoplasm and an eccentrically placed nucleus
  - 4-6 um
- Tachyzoites disseminate throughout the body after ingestion.
- They are phagocytosed by macrophages and neutrophils
Toxoplasma gondii

- Obligate intracellular parasite with three life forms: oocysts, tachyzoites and tissue cysts
- Complete life cycle only in felines
- Sporulated oocysts shed by cats can be infectious for > 1 year
- Tachyzoites disseminate throughout the body after ingestion.
- Around 50% of US adults have antibodies
**Toxoplasma gondii**
- Host immune response often leaves tissue cysts scattered in the body: brain, skeletal muscle and cardiac muscle.
- Reactivation with dissemination in immunocompromised individuals
- Cutaneous involvement is rare- several reported cases in literature in HIV-positive patients

**Leishmania- Morphologic Features**
- Amastigote: Small round-oval organism with eccentric nucleus
- Intracellular (macrophages) or extracellular
- Key to ID: rod shaped “kinetoplast” within each amastigote adjacent to the nucleus
- Does not stain with silver stain (GMS)
Leishmania- Epidemiology

- Parasite infection transmitted by infected sandflies (Promastigote circulates in blood)
- **Cutaneous Leishmaniasis**-
  - Afghanistan, Iran, Iraq, Saudi Arabia, Brazil, Peru
  - Skin ulcers, nodules (generally localized)
- **Viseral Leishmaniasis**-
  - India, Nepal, Sudan, Brazil
  - Enlarged liver, spleen, weight loss, fever, high mortality
- **Mucocutaneous (can occur post cutaneous or visceral)**
  - Severe form that involves sinus and nasal mucosa- can be disfiguring
- United States infection– travel history

Histoplasma- Morphologic Features

- Small round yeast forms (2-4 um)
- Intracellular location (macrophage) or extracellular location (within granulomatous debris)
- Pseudocapsule (clearing around each yeast)
- No kinetoplast
- Stain with silver stain (GMS)

Histoplasma
**Histoplasma capsulatum**

Peripheral Blood: Giemsa  
GMS

---

**Case 7**

Kinetoplast

Histoplasma  
Toxoplasma  
Leishmania

---

**My Diagnosis:**

**Cutaneous Leishmaniasis**

**Consider**

- Mucocutaneous given HIV status and “plaque-like” growth or
- Other rare forms: “Disseminated cutaneous leishmaniasis” (diffuse nodular non-ulcerating disease)
Case 7 - ASC Website Diagnoses

- Leishmaniasis
- Histoplasmosis
- Toxoplasmosis
- Kaposi Sarcoma

case 7 - Panelist’s Diagnoses

- Granulomatous inflammation with mycobacterium???? I’m not good with micro at all
- Cutaneous Histoplasmosis
- Cutaneous Leishmaniasis

skin biopsy
Case 7 - DIAGNOSIS
CUTANEOUS LEISMANIASIS
## Leishmaniasis

<table>
<thead>
<tr>
<th></th>
<th>Cutaneous</th>
<th>Visceral (kala azar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</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>Location</td>
<td>Africa, Middle East, southern Europe, Latin America</td>
<td>Asia, Middle East, Africa, Mediterranean basin</td>
</tr>
<tr>
<td>Clinical</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>

**Female sandfly**

- *Phlebotomus*, Eastern Hemisphere
- *Lutzomyia*, Western Hemisphere
Differential Diagnosis

HISTOPLASMOSIS

Histoplasma

Leishmania

Histoplasma

Leishmania
## Leishmaniasis vs. Histoplasmosis

<table>
<thead>
<tr>
<th></th>
<th>Leishmaniasis</th>
<th>Histoplasmosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMS, PAS</td>
<td>-</td>
<td>+</td>
</tr>
<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>
<td>present</td>
<td>absent</td>
</tr>
</tbody>
</table>

*Leishmaniasis, Brown-Hopps Gram*
• CL is endemic in the Middle East

• those with no immunity & new to the region are most at risk

• military personnel and civilians may return to U.S. before 1st clinical signs appear – incubation period up to several months
CASE 8

A 78 year-old hypothyroid woman presents with a 4cm heterogeneous left thyroid lobe nodule. She has had this nodule for 25 years. Prior FNAs (? number) have been benign, but these were prior to the more recent growth and records are not available.

FNA aspirate specimen:
Romanowsky smear and Pap stained Cytospin Preparation

CASE 8: What’s in the history?

78 yo woman
hypothyroid (etiology?)
4 cm heterogeneous (solid and cystic) nodule (25 years history)
prior FNAs (? number): BENIGN recent growth
CASE 8: Differential Diagnoses

Primary Thyroid Lesion
- spindle cell features
- hemorrhage
- cystic change
- background of non-neoplastic thyroid

(Benign/Reactive vs Malignant?)

Extrathyroidal Neoplasm (including parathyroid)

Metastasis
(spindle cell features-Carcinoma/Sarcoma/Melanoma)

CASE 8

Post-fine-needle aspiration spindle cell nodule
Benign nodule/cyst changes NOS: Cyst lining cells/granulation tissue/stromal fragments/squamous or spindle metaplasia etc.
Spindle cell adenoma
Medullary carcinoma
Papillary carcinoma
Anaplastic carcinoma
Hyalinizing trabecular tumor
Riedel thyroiditis
Fibrosing variant of Hashimoto thyroiditis
Fibromatosis
Solitary fibrous tumor
Lemymoma
Peripheral nerve sheath tumor
Follicular dendritic cell tumor
Sarcoma
Squamous cell carcinoma
Spindle epithelial tumor with thymus like differentiation (SETTLE)
Carcinoma showing thymus-like differentiation (CASTLE)
Case 8

- 78 y/o hypothyroid woman presents with a 4x4 cm. L thyroid nodule
- nodule present for 25 years
- prior FNAs (? number) presumably have been benign; records are not available
- more recent growth

Case 8 - ASC Website Diagnoses
case 8 - Panelist’s Diagnoses

• Suspicious for neoplasm. DDx includes mesenchymal neoplasm or unusual Hürthle cell neoplasm.

• PTC with nodular fasciitis stroma

• Fibrotic variant of Hashimoto Thyroiditis

cell-block

negative: TTF-1, cytokeratin AE1/3, CD34, SMA
case #8 - my FNA diagnosis

“Spindle Cell Lesion, possibly a Vascular Neoplasm”

total thyroidectomy
Case 8 - DIAGNOSIS

Post-FNA Spindle Cell Nodule of Thyroid (PSCNT)
(partially angiomatous & hyalinized)
Spindle Cell Lesions, Thyroid

- MTC
- ATC
- PTC with fascitis-like stroma
- follicular adenoma
- fibrous variant of Hashimoto thyroiditis
- spindle cell melanoma
- ectopic thymoma
- post-FNA spindle cell nodule
- solitary fibrous tumor
- schwannoma
- leiomyoma
- spindle cell sarcomas
  - synovial sarcoma
  - angiosarcoma
  - LMS
  - MPNST
- SETTLE

Post-Fine-Needle Aspiration Spindle Cell Nodules of the Thyroid (PSCNT)

Zubair W. Baloch, MD, PhD, Hong Wu, MD, PhD, and Virginia A. L'Volpe, MD

Key Words: Thyroid, Inflammation, pseudothymoma, spindle cell sarcoma de novo, nevus, non-thyroidal proliferation, post-FNA change

8 Cases
- Soft Tissue
- Cervix
- Body Cavity Fluid
- Thyroid
- Salivary Gland
- Skin