Fine Needle Aspiration Cytology of the Head & Neck: a kaleidoscope of problematic lesions (Workshop #2)

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Objectives of workshop
- To provide a structured approach for the resolution of differential diagnoses of problematic lesions in the Head & Neck region
- To increase awareness of the registrants with diagnostic pitfalls of the Head & Neck region
- To familiarize the registrants with the new diagnostic Bethesda System for reporting thyroid cytopathology

Problematic lesions of the H&N region
- Thyroid
  - Follicular lesions
  - Hurthle cell lesions
  - Atypia of undetermined significance
- Cystic lesions
- Lesions with atypical squamous cells
- Lymphoid lesions
- Salivary glands
  - Basaloid tumors of salivary gland
- Metastases
- Miscellaneous

Possible origin of neck masses
- Thyroid
- Parathyroid gland
- Lymph nodes
- Salivary gland
- Miscellaneous

Thyroid

CME FACULTY DISCLOSURE

Dr. M. Auger has no affiliation with the manufacturer of any commercial product or provider of any commercial service discussed in this CME activity.
Thyroid Nodules and FNAs

• Thyroid nodules are very common
  – 4-7% of adult population
• Most are benign
• Surgery for all thyroid nodules is not practical
• “FNA is the most accurate and cost effective method for evaluating thyroid nodules”


FNA biopsy of the thyroid:
An appraisal

• Review relevant articles on thyroid FNAs, 1982-1991
• Based on pooled data from 7 series
• (N=18 183)
  – Gardiner et al. Canada
  – Hawkins et al. Spain
  – Khafagi et al. Australia
  – Hall et al USA
  – Altavilla et al. Italy
  – Caplan et al. USA
  – Gharib and Goellner. USA

FNA biopsy of the thyroid: An appraisal

<table>
<thead>
<tr>
<th>Result</th>
<th>Pooled %</th>
<th>Range %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>69%</td>
<td>53-90%</td>
</tr>
<tr>
<td>Suspicious</td>
<td>10%</td>
<td>5-23%</td>
</tr>
<tr>
<td>Positive</td>
<td>4%</td>
<td>1-10%</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>17%</td>
<td>2-21%</td>
</tr>
</tbody>
</table>


Thyroid FNA diagnostic classifications

• Pathologists have varied widely in how they report thyroid FNAs
• This proliferation of reporting formats makes it difficult
  – To compare accuracy of data
    • Sensitivity
    • Specificity
    • PPV
    • NPV
  – For clinicians to interpret reports from other institutions

Wang HH. Diagn Cytopathol 2006, 34:67-76

• 87 publications: 1966-December 2004
• 2-category scheme 3/87 3%
• 3-category scheme 41/87 47%
• 4-category scheme 17/87 20%
• 5-category scheme 8/87 9%
• ≥ 6 category scheme 10/87 11%

Previous attempts at standardization

• Papanicolaou Society Task Forces
• American Thyroid Association (ATA)
• American Association of Clinical Endocrinologists (AACE)
• National Cancer Institute
  Thyroid FNA: State of the Science Conference
  October 22-23, 2007 (Bethesda, MD)
NCI thyroid conference

• The final version of the conclusions of the conference are published in articles in:
  – Diagnostic Cytopathology, Vol 36, No 6 (June 2008)
• An atlas, edited by Drs. Edmund Cibas and Syed Ali, published in December 2009

Diagnostic terminology for FNA diagnosis of thyroid lesions

<table>
<thead>
<tr>
<th>NCI Categories</th>
<th>Alternate category</th>
<th>Risk of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>0-3%</td>
<td></td>
</tr>
<tr>
<td>Atypia of undetermined significance/ Follicular lesion of undetermined significance (FLUS)</td>
<td>Follicular lesion of undetermined significance</td>
<td>5-15%</td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>Suspicious for follicular neoplasm</td>
<td>15-30%</td>
</tr>
<tr>
<td>– Specify if Hurthle cell neoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspicious</td>
<td></td>
<td>60-75%</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td>97-99%</td>
</tr>
<tr>
<td>Non-diagnostic</td>
<td></td>
<td>unsatisfactory</td>
</tr>
</tbody>
</table>

Non-diagnostic/unsatisfactory

• Although both terms are used as synonyms in some institutions, they have a different significance in others
• Unsatisfactory: cannot give any useful information
  – Acellular or virtually acellular specimen
  – Cellular but cannot see anything because of blood or air-drying artefact
• Non-diagnostic: can provide some partial information
  – Cyst contents
What to do an FNA containing abundant colloid and little else?

- Because such FNAs most likely represent colloid nodules and carry an insignificant risk of malignancy, they can be included in the benign category as being
  - "suggestive of colloid nodule"

Exceptions to the adequacy requirements

- FNA containing abundant thick colloid (i.e., slide full of colloid) and little else
  - One of the "hot" topics at NCI conference
- Any specimen with any atypical features, even if not meeting adequacy criteria, cannot be called non-Dx/unsat
  - Should be placed in atypical category
- Lymphocytic thyroiditis
  - As may occasional yield only lymphocytes with few follicular cells

Adequate (satisfactory) sampling of solid and cystic lesions

- All thyroid FNAs must be technically adequate, with well-preserved and well-prepared thyroid follicular epithelial cells for interpretation

What to do an FNA containing only (or mostly) macrophages?

- Another "hot topic" at NCI
- Where best to categorize them?
  - Benign?
  - Unsatisfactory?
  - Non-diagnostic?
- If cyst is simple, non-complex
  - Risk of malignancy: 1-4%
- If mixed (solid, cystic nodules), large (> 3 cm), or recurring
  - Risk of malignancy: up to 14%
Non-diagnostic specimen

- The conclusion was that cystic specimens containing macrophages only (or macrophages with < than 6 groups of follicular cells) should be diagnosed as “non-diagnostic: cyst fluid only” with a recommendation that correlation should be made with the US findings; an optional disclaimer that cystic carcinoma cannot be excluded may be added.
- Non-diagnostic because can provide some partial information
  - Cyst contents
    - but cannot state the underlying nature of the cyst
      - nodular goiter?
      - cystic papillary carcinoma?

What constitutes an unsatisfactory specimen?

- This term should be reserved to specimens
  - of limited cellularity (ie. < 6 groups of follicular epithelium)
  - containing no follicular epithelium, or
  - of poor preservation precluding cellular evaluation

Case: clinical Hx

- FNA of thyroid nodule in a 44 y.o. woman
Case: Differential Dx of “cellular follicular lesion”

- Benign: nodular goiter in hyperplastic phase
- Follicular neoplasm
- Atypia of undetermined significance (AUS)

Case: Final DX

- Benign
- Most consistent with nodular goiter in hyperplastic phase

Algorithm for evaluation

Adequate

No

Evaluate ARCHITECTURE

- Mainly honeycomb – non-neoplastic
- Mainly syncytial – neoplastic

Evaluate NUCLEI

- Nuclei follicular lesion – Nodular goiter
- Nuclei papillary ca – Papillary carcinoma
- Nuclei follic. lesion – Follicular neopl.
Nodular goiter I

Benign.
Fragments of follicular epithelium present, mostly in honeycomb arrangement, admixed with colloid, most consistent with NODULAR GOITER.

Nodular goiter II

Benign.
Fragments of follicular epithelium present, mostly in honeycomb arrangement, admixed with colloid and foamy macrophages, most consistent with NODULAR GOITER WITH CYSTIC DEGENERATION.
Nodular goiter III

Benign.
Abundant fragments of follicular epithelium present, mostly in honeycomb arrangement, admixed with colloid, most consistent with NODULAR GOITER IN HYPERPLASTIC PHASE

Follicular neoplasms

Follicular neoplasms

• Differential diagnosis
  – follicular adenoma
  – follicular carcinoma
AUS-Follicular lesion of undetermined significance (FLUS)

Atypia of Undetermined Significance

- Heterogeneous category of cases
  - Cytological findings are not convincingly benign, yet the degree of cellular or architectural atypia is not sufficient for an interpretation of "follicular/Hurthle neoplasm" or "suspicious for malignancy"
  - Some cases: because of compromised specimen
    - Low cellularity
    - Poor fixation
    - Obscuring blood
- Should represent <7% of all thyroid FNAs
  - This is questionable according to recent studies (range 3-18%)
- Risk of malignancy 5-15%

Atypia of Undetermined Significance-definition

- Reserved for specimens that contain cells (follicular, lymphoid, or other) with architectural and/or nuclear atypia that is not sufficient to be classified as suspicious for a follicular neoplasm, suspicious for malignancy, or malignant
- On the other hand, the atypia is more marked that can be ascribed confidently to benign changes

Atypia of Undetermined Significance

- A contributing factor to the uncertainty is often (but not always) a compromised specimen
  - Sparsely cellular
  - Obscured by blood or excessive clotting
- The term "Follicular lesion of undetermined significance" (FLUS) is equally acceptable in the majority of cases in which the atypia is of follicular origin (not lymphoid or other)

AUS-Criteria (FLUS)

- Predominance of microfollicles in a sparsely cellular FNA with scant colloid, or
  - More prominent than usual population of microfollicles (and may be disproportionately apparent on a minority of smears) in a moderately to markedly cellular specimen
- Interpretation of follicular cell atypia is hindered by sample preparation artefact
  - Air-drying artefact with slight nuclear and cytoplasmic enlargement, pale and slightly smudgy chromatin, and/or mildly irregular nuclear contours
- Clotting artefact with apparent cellular crowding

AUS-criteria (other)

- A minor population of follicular cells show nuclear enlargement, often accompanied by prominent nucleoli
  - FNA from patients with a history of radioactive iodine, or other pharmaceutical agents
  - Repair due to involutional changes such as cystic degeneration and/or hemorrhage
- There is an atypical lymphoid infiltrate (in which a repeat FNA for flow cytometry would be desirable), but the degree of atypia is insufficient for the category "suspicious for malignancy"
- Not otherwise categorized
Atypia of Undetermined Significance

- Follicular lesion of undetermined significance (FLUS)
  - Hurthle cell lesion of undetermined significance
- Suboptimal specimens
- Other atypical lesions (should be specified in the diagnosis)

Atypia of undetermined significance

- Grey zone follicular/Hurthle cell lesions (hyperplasia vs neoplasia)
- Suboptimal specimens
  - Air-drying
  - Clotting
  - Low cellularity
- Atypical cyst-lining/mesenchymal cells (repair)
- Therapy changes
- Other nonspecific changes that cause concern

Atypia of undetermined significance

- Architectural atypia
- Compromised specimen
- Cytologic atypia

AUS-sample report

- Atypia of undetermined significance
  - Sparsely cellular aspirate comprised of follicular cells with architectural atypia. Colloid is absent.
  - Note: a repeat FNA after an appropriate interval of observation may be helpful if clinically indicated

AUS-sample report

- Atypia of undetermined significance
  - Follicular cells, predominantly benign-appearing, with focal cytologic atypia.
  - Note: a repeat FNA after an appropriate interval of observation may be helpful if clinically indicated
AUS-sample report

- Atypia of undetermined significance
- Follicular cells with focal cytologic and architectural atypia, but obscuring blood and clotting artifact preclude definitive diagnosis.
- Note: a repeat FNA after an appropriate interval of observation may be helpful if clinically indicated.

AUS-sample report

(in a pt treated with radioiodine)

- Atypia of undetermined significance
- Marked cytologic atypia of follicular cells.
- Note: In a patient treated with radiiodine, the findings likely represent reactive, treatment-related changes, but a neoplasm cannot be entirely excluded. Clinical correlation is advised.

Case: clinical Hx

- FNA of thyroid nodule in a 69 y.o. woman

Hurthle cell lesions
Case

• What is your differential diagnosis?

Case: Ddx

• Hurthle cell neoplasm
• Benign: Hurthle cell metaplasia in a non-neoplastic lesion
• AUS

Case: Final DX

• Follicular neoplasm, Hurthle cell type

Hurthle cell lesions

Differential diagnosis
• Hurthle cell metaplasia in non-neoplastic lesion
  – Nodular goiter
  – Lymphocytic thyroiditis
• Hurthle cell metaplasia in neoplastic lesion
  – Papillary carcinoma
• Hurthle cell neoplasm
Algorithm for Hurthle cell lesions

Evaluate ARCHITECTURE

- Mainly honeycomb ~ non-neoplastic
- Mainly syncytial ~ neoplastic

Hurthle cell metaplasia
Hurthle cell neoplasm

**Algorithm for Hurthle cell lesions**

**Lymphocytic thyroiditis**

**BENIGN.**
Fragments of follicular epithelium present, some with Hurthle cell changes, admixed with lymphocytes, most consistent with LYMPHOCYTIC THYROIDITIS.

**Cytologic criteria in Hurthle cell neoplasm I**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Favor neoplasm</th>
<th>Favor non-neoplastic</th>
<th>Not helpful</th>
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<tbody>
<tr>
<td>Hypercellularity</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Predominance Hurthle cells</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Monomorphism</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Large pleom. nuclei/nucleoli</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Architecture</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dyscohesion</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

N=no references; modified from Renshaw, Cancer Cytopathology 98:261, 2002

**Cytologic criteria in Hurthle cell neoplasm II**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Favor neoplasm</th>
<th>Favor non-neoplastic</th>
<th>Not helpful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncytia/crowding</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Transgression of vessels</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracytoplasmic inclusions</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrophages</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

N=no references; modified from Renshaw, Cancer Cytopathology 98:261, 2002

**Papillary carcinoma versus Follicular neoplasm, Hurthle cell type**
FNAC differential Dx oncocyic lesions

<table>
<thead>
<tr>
<th>FNAC features</th>
<th>Oncocytic papillary CA</th>
<th>Oncocytic follicular neopl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear inclusions</td>
<td>50%</td>
<td>12%</td>
</tr>
<tr>
<td>Nuclear grooves</td>
<td>80%</td>
<td>12%</td>
</tr>
<tr>
<td>Prominent nucleoli</td>
<td>Absent</td>
<td>57%</td>
</tr>
</tbody>
</table>

% of cases positive. Moreira et al. Acta Cytol 48:137, 2004

Medullary carcinoma versus Hurthle cell neoplasm

AUS-FLUS (Hurthle cell type)
AUS-sample report

- Atypia of undetermined significance
  - Sparsely cellular aspirate comprised of Hurthle cells with architectural atypia. Colloid is absent.
  - Note: a repeat FNA after an appropriate interval of observation may be helpful if clinically indicated

AUS-sample report
(in a pt with multiple nodules)

- Atypia of undetermined significance
  - The specimen is moderately cellular and consists almost exclusively of Hurthle cells. Colloid is scant, and there is no apparent increase in lymphocytes.
  - Note: In a patient with multiple nodules, the findings likely represent a Hurthle cell hyperplasia in the setting of multinodular goiter, but a Hurthle cell neoplasm cannot be entirely excluded. Clinical correlation is advised.

AUS-sample report
(in a pt with history of Hashimoto thyroiditis)

- Atypia of undetermined significance
  - The specimen consists almost exclusively of Hurthle cells.
  - Note: In a patient with Hashimoto thyroiditis, the findings likely represent a Hurthle cell hyperplasia, but a Hurthle cell neoplasm cannot be entirely excluded. Clinical correlation is advised.

Nuclear atypia in Hurthle cells

- Marked nuclear atypia can be seen in many benign oncocytic lesions
  - Lymphocytic thyroiditis
  - Graves’ disease
  - Longstanding nodular goiter
  - Atypical Hurthle adenoma

Case: clinical Hx

- Neck cystic nodule
  in 25 y.o. man
Case: final Dx

- Cyto Dx:
  - Negative for malignant cells.
  - Cytological features most consistent with THYROGLOSSAL DUCT CYST

Thyroglossal duct cyst

- Results from failure of obliteration of thyroglossal duct following descent of the thyroid in 6th week of fetal life
- During the 8-10th weeks of fetal life, the duct normally undergoes complete involution

Thyroglossal duct cyst: clinical features I

- Most often results in firm painless, nodule in midline neck
  - But can also occur laterally or intrathyroidally as a discrete mass, simulating a primary thyroid gland lesion
- Most common in children; but can also be found in adults

Thyroglossal duct cyst: cytology

- Colloid 61%
- Macrophages 89%
- Lymphocytes 72%
- Neutrophils 61%
- Ciliated columnar cells 33%
- Metaplastic squamous cells 33%


Thyroglossal duct cyst: cytology

- Immature metap. sq. cells 22%
- Anucleated squames 16%
- Parakeratotic cells 16%
- Thyroid epithelium 11%
- Proteinaceous debris 16%
- Granular and cystic debris 11%

DDX of cystic lesions in neck region

- Non-neoplastic
  - Thyroglossal duct cyst
  - Branchial cleft cyst
  - Epidermal cyst
  - Thyroid gland cyst
- Neoplastic
  - Thyroid: papillary carcinoma
  - Lymph node: metastatic CA (esp. squamous CA, thyroid papillary CA)
  - Salivary gland origin: Warthin tumor, pleomorphic adenoma, mucoepidermoid CA

Important information to resolve DDX of cystic lesions in neck

- Location
  - Midline vs. lateral
- Age of patient
- Significant past history

Non-diagnostic specimen

- Specimen consists largely of foamy macrophages, consistent with cyst content.
- In view of the absence/scant amount of epithelium, the underlying nature of the cyst cannot be determined.
- Recommend additional material (re-aspiration?) if clinically indicated.

Branchial cleft cyst vs. thyroglossal duct cyst (TDC)

- Branchial cleft cyst
  - Usually lateral (vs. midline for TDC)
  - Usually more cellular
    - Squamous epithelium (nucleated and anucleated)
    - Cholesterol crystals
    - Amorphous debris
    - Numerous lymphocytes
Branchial cleft cyst: cytology I

- Proteinaceous material, mucus
- Foam cells
- Epithelial cells usually sparse
  - squamous (immature squamous to superficial-like mature, degenerated keratinized)
  - glandular (goblet, mucous, ciliated)

Branchial cleft cyst: cytology II

- Lymphoid tissue (germinal centers, tingible-body macrophages)
- Acute inflammation
- Granulation tissue
- Granulomatous reaction (to keratin)

Branchial cleft cyst vs. metastatic squamous CA

- DDx from well-diff squamous CA can be very difficult
  - Squamous CA usually contains at least a few cells with clear-cut malignant features
  - Look for a less-differentiated, nonkeratinizing, malignant component
  - Clinically, usually in patients over 50

Epidermal inclusion cyst

- Epidermal inclusion cyst
  - thicker, semi-solid paste-like material
  - mostly anucleated squames
Benign lymphoepithelial cyst
- May be due to duct obstruction related to lymphoid hyperplasia in parotid gland
- When seen in HIV patients, are usually multiple and bilateral
- Cytology: similar to branchial cleft cysts

Atypical cells present; cannot rule out papillary carcinoma

AUS vs suspicious for PTC
- Separation of AUS from the suspicious for malignancy category is problematic for FNAs with focal features of PTC
- AUS best reserved for those rare cases with few cells with distinct but mildly atypical nuclear features
- Distinction may be difficult
- Expert consultation may be warranted in especially challenging case
AUS-sample report

- Atypia of undetermined significance
  - Numerous relatively monomorphic lymphoid cells.
  - Note: The findings are atypical and raise the possibility of a lymphoproliferative lesion, but immunophenotyping studies could not be performed because of insufficient material. An additional FNA, with apportioning of fresh needle-rinse fluid for flow cytometry, might be helpful if clinically indicated.

Lymph nodes

Case: clinical Hx

- 55 y.o. F
- In 2001, presented with superior vena cava syndrome
- Diagnosis made and she was treated
- In 2003, left Virchow node
- FNA to rule out recurrent disease

Case: Immunohistochemistry

- Immunohistochemistry positive for:
  - Cytokeratin CAM5.2 + AE1
  - Synaptophysin
- Immunohistochemistry negative for:
  - CD45
  - CD3, CD43, CD45RO
  - CD20
  - Chromogranin
Case: final Dx
• Recurrent small cell carcinoma, from previous pulmonary primary
• Confirmed by immunohistochemistry
• No biopsy performed

Cytological assessment of lymph node
• First, rule out metastasis
  – Small cell carcinoma
  – Squamous cell carcinoma
  – Nasopharyngeal carcinoma
  – Adenocarcinoma

Case: clinical Hx
• 28 y.o. woman presents with enlarged left cervical lymph node
• FNA and subsequent biopsy performed
Case: cytological diagnosis

- Reactive polymorphic population of lymphoid cells with tingible-body macrophages, consistent with reactive process

Introduction: FNA of lymph nodes

- Traditionally aimed at detection of metastasis
- Use in lymphoproliferative disorders controversial
  - Particularly in the primary diagnosis of lymphoma
  - Better accepted for staging, Dx of recurrent or residual disease

Introduction: FNA of lymph nodes

- Reasons for unpopularity
  - On pure morphologic grounds, some lymphomas and reactive hyperplasias indistinguishable
  - Cannot distinguish growth patterns
    - Nodular or follicular vs. diffuse
    - Mantle, marginal zone

Advances applicable to cytological Dx of lymphomas

- Development of antibodies allowed a combined morphological and immunocytochemical approach
- W.H.O. classification (2001) emphasizes the diagnostic importance of
  - Cytomorphology in addition to the architectural pattern
  - Immuno-phenotyping
  - Molecular biological and genetic data
Indications for cytological assessment of lymphoid lesions

- Establish the nature of the mass
  - Lymphoproliferative
  - Metastatic carcinoma
  - Granulomatous
- Triage patients requiring excisional biopsy versus those best followed-up clinically
- Guide selection of optimal lymph node for excision

Indications for cytological assessment of lymphoid lesions

- Diagnostic tool in superficial and deep sites in poor surgical candidates
- Establish lymphomatous nature of a mass that subsequently may serve as marker for response to Rx
- Staging of lymphoma
- Evaluation of patients with known lymphoma and recurrent masses
- Obtain additional material for ancillary studies

FNA Dx of lymphoid lesions: pros

- Surgical biopsy may not always be best approach
  - If no superficial lymph nodes available
  - If biopsy becomes major invasive procedure
- Rapidity and minimal invasiveness to provide accurate Dx in highly proliferative lymphomas (e.g. Burkitt) may be of critical clinical importance

FNA of supraclavicular node from 54 y.o. M

Immunocyto/histochemistry

- Pros
  - Lesser numbers of cells required
  - Clear morphology of cells expressing Ag
- Cons
  - Quantitation of Ag more subjective

Cons

- Requires more cells
- No morphology of cells expressing Ag

Flow cytometry

- Pros
  - Quantiﬁcation of Ag more objective
  - Easier to detect abnormal co-expression of Ag
- Cons
  - Requires more cells
  - No morphology of cells expressing Ag

Cytological Dx of lymphoid lesions

- On-going cyto-histological correlation essential
- Recognize limitations: try not to be too heroic
- Try to collaborate with (or marry) a “lymphomaniac”
  - Use a consultant in difficult cases
- Bottom-line: use common sense
Granulomatous inflammation
• Known cause of false-positive diagnoses
• Relatively infrequently encountered
• Its epithelioid “look” can be mistaken for carcinoma

Cytology
– clumps of epithelioid macrophages
– lymphocytes ± multinucleated giant cells
– background: usually lymphocytes ± acute inflammation
– special stains for fungi and acid-fast bacilli

Cytological assessment
• After R/O metastasis, evaluate cell composition
  – polymorphous versus monomorphous
• Look for
  – tingible-body macrophage
  – plasma cell
  – granuloma
  – Hodgkin and Reed-Sternberg cell

• Cell size
  – Small: < 2x size small lymphocyte or < size histiocyte nucleus
  – Intermediate: ≈ 2x size small lymphocyte (for some 2-3x) or ≈ size histiocyte nucleus
  – Large: > 2x size small lymphocyte (for some >3x) or > size histiocyte nucleus

• Nuclear shape
  – Round
  – Cleaved
  – Lobulated

Monomorphous lymphoid processes
• Small cells: CLL/SLL, follicular grade 1, mantle cell, marginal zone
• Intermediate cells: Burkitt, lymphoblastic
• Large cells: large cell (± immunoblastic), anaplastic

Polymorphous processes
• Reactive lymphoid hyperplasias
• Hodgkin lymphomas
• T-cell lymphomas
• Follicular lymphomas, grade 2, ± 3
DDx

• Intermediate lymphocytes
  – Burkitt lymphoma
  – Lymphoblastic lymphoma
  – Mantle cell lymphoma, blastoid variant

• Large lymphocytes
  – Large cell lymphoma
  – Follicular lymphoma, grade 3
  – Anaplastic large cell lymphoma
  – Peripheral T-cell lymphoma (some)

• Mixed
  – Follicular lymphoma, grade 2
  – Peripheral T-cell lymphoma (most)

  • DDx: reactive, Hodgkin lymphoma

Initial immunochemistry panel for cytology

• If a lymphoid cell population
  – CD3
  – CD20
  – CD43
  – CD45RO

Reactive lymphoid hyperplasia

• Polymorphous population
  – Small and large lymphocytes
  – Tingible-body macrophages
  – Plasma cells, sometimes

DDx reactive lymphoid hyperplasia

• Follicular lymphoma, grade 2 (mixed small cleaved and large cell)
  – Lacks plasma cells, immunoblasts, tingible-body macrophages
  – Immunohistochemistry: almost exclusively B cells (vs. reactive, typically T-cell predominance)

Reactive lymphoid hyperplasia

• If cell block, do immunocytochemistry
  – Typically, predominantly T cells: pattern re-assuring, supports Dx
  – If equivocal (i.e. no clear T-cell predominance)
  
    Dx = “atypical lymphoid population” - recommend excisional biopsy (if clinically indicated)

Reactive lymphoid hyperplasia: cytology

• Typical
  – Combination of mature and immature lymphocytes results in a highly characteristic range of maturation with a predominance of small lymphocytes

• Atypical
  – Any FNA in which small mature lymphocytes do not predominate is suspicious for malignancy
  – BUT, although unusual for large cells to dominate in benign lymph nodes, marked follicular hyperplasia can show focal high proportion of large cells
Cytology sign-out of “negative” lymph node

- No evidence of metastasis seen
- Polymorphous lymphoid population present, most consistent with BENIGN/REACTIVE LYMPH NODE

COMMENT: Recommend follow-up and excision of the node if it persists for more than two (2) months or if it enlarges further, if clinically indicated

Before jumping to a Dx of lymphoma in cytology

- **Make sure to rule out:**
  - metastasis
  - granulomatous inflammation
  - lymphoid hyperplasia

Small cell lymphoid lesions: DDx

- Chronic lymphocytic leukemia (CLL)
- small lymphocytic lymphoma (SLL)
- Lymphoplasmacytic lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Marginal zone lymphoma

- Many cytologically similar, but different biological behaviors
- Distinction based primarily on differences in immuno-phenotypes

DDx

- Intermediate lymphocytes
  - Burkitt lymphoma
  - Lymphoblastic lymphoma
  - Mantle cell lymphoma, blastoid variant

- Large lymphocytes
  - Large cell lymphoma
  - Follicular lymphoma, grade 3
  - Anaplastic large cell lymphoma
  - Peripheral T-cell lymphoma (some)

- Mixed
  - Follicular lymphoma, grade 2
  - Peripheral T-cell lymphoma (most)
  - DDx: reactive, Hodgkin lymphoma

Low-grade B-cell lymphomas I

<table>
<thead>
<tr>
<th>Type</th>
<th>Cytology</th>
<th>Immunochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLL/CLL</td>
<td>Small, round clumped chromatin prolymphocytes, parainmunoblasts.</td>
<td>CD20+(dim), CD5+, CD19+, CD23+, CD10-, CyclinD-, CD43+</td>
</tr>
<tr>
<td>Follicular</td>
<td>Mixed small, cleaved, notched centrocytes+ large non-cleaved centroblasts</td>
<td>CD20+, CD10+, CD23+/-, CD5+, CyclinD-CD43-</td>
</tr>
</tbody>
</table>

Low-grade B-cell lymphomas II

<table>
<thead>
<tr>
<th>Type</th>
<th>Cytology</th>
<th>Immunochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantle cell lymphoma</td>
<td>Monomorphic, small irregular cells, clumped chromatin few blastoid cells</td>
<td>CD5+, CD19+, CD20+, CyclinD+, CD43+, CD10-, CD23-</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>Small, round cells, scattered immunoblasts plasmacytoid cells</td>
<td>CD5+, CD10–, CD19+, CD20+, CD23–, CyclinD–, Bcl2+/–, CD43–/+</td>
</tr>
</tbody>
</table>
Follicular lymphoma: cytology

- Represent approximately 25% of B-cell NHL
- Cytology is mixture of
  - small cleaved cells
  - large cleaved cells
  - large non-cleaved cells
- Centrocytes (small cleaved cells)
  - Slightly larger than small, mature lymphocytes
  - Highly irregular nuclear outlines (twisted)
  - Condensed chromatin
  - Inconspicuous/absent nucleoli

Large B-cell lymphoma: cytology

- Comprise ~ 34% of NHL
- Heterogeneous entities, but significant component of large cells
- Variants
  - Centroblastic
  - Immunoblastic
  - Anaplastic
  - T-cell rich
- Morphology centroblastic variant
  - Round nuclear outlines
  - Vesicular chromatin
  - Single to multiple prominent nucleoli, hugging nuclear membrane

Follicular lymphoma: cytology

- Large centrocytes (large cleaved cells)
  - Morphology similar to small cleaved cells
  - Irregular nuclei >2-3x size of small lymphocyte, fine chromatin
  - absent or inconspicuous small nucleoli
- Centroblasts (large non-cleaved cells)
  - Size = larger than large cleaved cells
  - Round nuclear outlines
  - Vesicular chromatin
  - Single/multiple prominent nucleoli at nuclear membrane

Lymphoblastic lymphoma: cytology

- Monomorphic population of medium-sized lymphocytes
- May be non-convoluted or convoluted
- Unlike large cell lymphoma
  - less pleomorphism
  - nucleoli inconspicuous
- Unlike low-grade lymphoma
  - very fine blast-like chromatin
  - frequent mitoses

Large B-cell lymphoma, immunoblastic morphologic variant: cytology

- Predominance (~ 90%) immunoblasts
  - Large round vesicular nuclei
  - Single prominent large central nucleolus
  - Cytoplasm abundant, plasmacytoid or clear

Precursor lymphoblastic leukemia/lymphoma

Epidemiology

- Lymphoblastic leukemia (ALL)
  - 80-85% B-cell
    - 75% occur in children < 6 y.o.
  - 15-20% T-cell
    - M > F, adolescents > children
    - 25% of cases of adult ALL are T-cell
- Lymphoblastic lymphoma
  - ~ 90% T-cell, more frequent in adolescent M
  - ~ 10% B-cell, 75% < 18 y.o., 88% < 35 y.o.
Lymphoblastic lymphoma

• Usually presents with
  – Symptomatic mediastinal mass
  – Pleural or pericardial effusion or
  – Supradiaphragmatic
    lymphadenopathy

• progresses rapidly to involve
  peripheral blood, bone marrow,
  CNS, gonads

Lymphoblastic lymphoma: immunohistochemistry

• Nuclear TdT+ in ~100%
• Generally negative for CD34
• B-cell lineage (15%)
  – Most CD19+, CD10+, CD79a+ (cytoplasm)
  – CD45 may be absent
  – 50% are CD20+ (mature ones only)

• T-cell lineage (85%)
  – Most freq. CD3+ (cytoplasm-specific)
  – Variable CD7, CD5, CD4, CD8+
  – May express CD79a

Classical Hodgkin lymphoma

Cytology of nodular sclerosis and mixed
cellularity

• Classic R-S cells
  – Bi- or multi-lobed nuclei
  – Prominent inclusion-like nucleoli
  – Moderately abundant cytoplasm

• Hodgkin mononuclear cells, lacunar cells

• Polymorphous background
  – Small reactive round lymphocytes, histiocytes
  – Eosinophils, plasma cells

FNA in Hodgkin lymphoma

• Limited value in primary Dx,
  sub-classification
• Very useful in Dx of
  recurrent disease

Hodgkin lymphoma: cytology

• In general, more difficult to diagnose
  than Non-Hodgkin lymphoma
• Immunocytochemistry helpful
  – CD15+, CD30+

• DDx
  – Peripheral T-cell lymphoma
  – Anaplastic large cell lymphoma
  – Reactive lymphoid hyperplasia
Classical Hodgkin lymphoma
Cytology of nodular sclerosis and mixed cellularity

- **Classic R-S cells**
  - Bi- or multi-lobed nuclei
  - Prominent inclusion-like nucleoli
  - Moderately abundant cytoplasm
- **Hodgkin mononuclear cells, lacunar cells**
- **Polymorphous background**
  - Small reactive round lymphocytes, histiocytes
  - Eosinophils, plasma cells

Hodgkin lymphoma: DDx

- Metastatic carcinoma
- Melanoma
- Germ cell neoplasm
- Reactive lymph node
- Non-Hodgkin lymphoma
- Sarcoma

Classical Hodgkin lymphoma
Immunohistochemistry

- **CD30+ in majority**
- **CD15+ in 75-85%**
- **CD20+ in up to 40%, but usually minority of cells and weak**
- **T cell markers usually negative**
- **CD45-, EMA-**

Anaplastic large cell lymphoma

- Definition
  - T-cell lymphoma composed usually of large lymphoid cells with abundant cytoplasm, pleomorphic nuclei often in horseshoe shape
- **Epidemiology**
  - 3% adult, 10-30% childhood NHL
  - High M:F in 2nd, 3rd decades

- Sites on involvement
  - Frequent nodal and extranodal sites, esp. skin, bone, soft tissue, lung, liver
  - Less gut, CNS, mediastinum
  - Bone marrow involved in 10% (up to 30% with CD30, ALK or EMA stain!-single cells)
- Most patients present with stage III/IV disease and B symptoms

Anaplastic large cell lymphoma

- **Histology**
  - Diffuse proliferation
  - If partial nodal involvement, growth in sinuses, in metastatic carcinoma-like fashion
- **Cytology**
  - Highly anaplastic multilobated or multinucleated, wreath cells
  - Hallmark and donut cells
Anaplastic large cell lymphoma

- **Immunohistochemistry**
  - CD30+, EMA+, 60-85% ALK+
  - Variable T-cell Ag+ (some null)
- **Molecular changes**
  - ≈ 90% clonal rearrangement TCR genes, even if null phenotype
  - Associated with t(2;5), between ALK gene on chr. 2 and nucleophosmin (NPM) gene on chr. 5 or other translocations

Limitations of FNAs

- Sampling error
- Insufficient material for immunohistochemistry
- Partial involvement by lymphoma
- Composite lymphoma
- Hodgkin lymphoma
- Rare non-lymphoid neoplasms
  - Langerhans cell histiocytosis
  - Dendritic cell neoplasms
  - Granulocytic sarcoma
- Provide no information on architecture

Sensitivity/specificity of lymphoma Dx by cytology

- Data vary by institution, with wide range
  - Sensitivity up to 80%
  - Specificity up to 95%
- **Lower if**
  - Hodgkin lymphoma included
  - Flow cytometry not performed

FNA of lymph nodes

- Many cases of lymphomas can be diagnosed and subclassified by cytology with adequate immunophenotypic information
- In the cytology of lymphoproliferative disorders, a combined morphologic and immunocytochemical approach is essential
- Cytology has a role to play in routine work-up of patients with lymphadenopathy or with known lymphoma

FNA of neck mass in 50 y.o. Inuit woman
• Diagnosis
  – metastatic non-small cell carcinoma
  – (c/w nasopharyngeal carcinoma)

Nasopharyngeal carcinoma
• DDX:
  – non-Hodgkin lymphoma
  – seminoma, dysgerminoma
  – melanoma

Case: clinical Hx
• FNA of a left neck mass in a 73 y.o. man
• no significant past medical history
Case: final Dx

- Cyto Dx:
  Anaplastic tumor most consistent with THYROID ANAPLASTIC CARCINOMA

Thyroid anaplastic carcinoma: cytology

- Cell types include:
  - Giant cell
  - Spindle cell
  - Squamoid cell

Thyroid anaplastic carcinoma: immunohistochemistry

- Positivity for
  - Cytokeratin: 40-100%
  - CEA: 10% (esp. squamoid)
  - Thyroglobulin: rarely (9%)
  - TTF-1: rarely (34%)

Salivary glands

Introduction

- Useful information from FNAs
  - Salivary gland
    - vs. lymph node vs. other?
  - Neoplastic vs. inflammatory
  - Benign vs. malignant? Exact type?
  - Selection of therapy
    - Antibiotics?
    - Surgery, extent?
    - Radiation, chemotherapy?
    - No therapy?
Salivary gland cysts
- Non-neoplastic
- Neoplastic
  - Pleomorphic adenoma
  - Warthin tumor
  - Low grade mucoepidermoid carcinoma
  - Acinic cell carcinoma
  - Metastatic squamous carcinoma

Salivary gland neoplasms
- Relatively uncommon, <2% of tumors in humans
- Site of origin
  - ~85% arise in the parotid
  - most of remainder arise in submandibular gland
  - very small proportion in sublingual and minor salivary glands
- Benign vs. malignant
  - 65-80% neoplasms in parotid are benign
  - 35-50% neoplasms in the other major and minor salivary glands are malignant

Pleomorphic adenoma
- Most common salivary gland neoplasm, accounting ~75% of all tumors in parotid gland (with as many as 90% occurring in superficial lobe)
- Pleomorphic adenoma ~10X more common in parotid than submandibular gland (2nd most common site)
- Rarely seen in sublingual or minor salivary glands
- F:M up to 4:1
Pleomorphic adenoma-Pitfalls

- Hypercellularity
  - ddx: other basaloid tumors
- Epithelial atypia
- Myoepithelial cell predominance
  - like fibroadenomas in the breast: keep it a low power DX
- Metaplastic changes
  - Squamous
  - Mucinous
  - Oncocytic
  - Spindle cell

Pleomorphic adenoma-Pitfalls

- Foci of squamous metaplasia (especially if atypical, e.g. with infarction) misinterpreted as mucoepidermoid carcinoma
- On occasion, lumens of the ducts distended with metachromatic mucin forming mucoid or hyaline globules that mimic adenoid cystic carcinoma
- Foci of mucous or goblet metaplasia also may mimic mucoepidermoid carcinoma

Benign Epithelial Tumours (other than pleomorphic adenomas)

- Characteristically show little or no stromal component
- Usually in parotid gland
- Subtypes include
  - Warthin tumour
  - Oncocytoma
  - Basal cell adenoma
  - Myoepithelioma

Mucoepidermoid carcinoma

- Represents 5-10% of all salivary gland neoplasms but 30% of malignant ones
- Most common primary malignant tumor of the parotid, but only 2nd most common primary malignant tumor in all other salivary glands (after adenoid cystic carcinoma)
- Histologically divided into low and high grade
  - Low-grade CAs tend to recur
  - High-grade CAs often metastasize
Adenoid cystic carcinoma
- Accounts for 2-5% of all tumors of parotid gland, but 15 and 30% of those in submandibular and minor salivary glands respectively
- Slowly growing, stubbornly recurrent
- Strong propensity to invade nerves
- Tendency to hematogenous dissemination (about 45%)

DDX of classic adenoid cystic carcinoma; ie. basaloid tumors
- Tumors with hyaline globules
  - pleomorphic adenoma
  - basal cell adenoma
  - polymorphous low-grade adenocarcinoma
  - epithelial-myoepithelial carcinoma

Polymorphous low-grade adenocarcinoma (PLGA)
- Recognized as a separate entity in early 1980s
- Occurs almost exclusively in minor salivary glands
- Slow-growing; can be associated with multiple recurrences over a number of years

PLGA
- **Histology**
  - Infiltrative growth pattern
  - But mixed architectural pattern: solid, glandular, cribriform, ductular, trabecular, papillary, cystic
  - Bland uniform cytology

**Cells**
- Very uniform
- Cuboidal to columnar in shape with ovoid to spindle-shaped nuclei
- Vesicular chromatin
- Small indistinct nucleoli
- Modest amount of pale eosinophilic cytoplasm which may be focally clear
**PLGA**

- **Cytology**
  - Few reports in literature
  - Cellular aspirates with sheets, acinar or papillary structures
  - Can have hyalin balls

- **Vs benign epithelial tumours (other than pleomorphic adenomas)**
  - PLGA: almost exclusively in minor salivary glands
  - (Unlike benign epithelial tumours which tend to occur in lower lip or major salivary glands)

- **Vs adenoid cystic carcinoma**
  - PLGA: nuclei smaller and more bland, hyaline balls usually smaller and granular, can have papillary formations

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**Adenoid cystic carcinoma vs Pleomorphic adenoma**

- Hyaline globules: frequency, size
- Ground substance: fibrillar
- Epithelial/mesenchymal relationship: "sunburst pattern"
- GFAP staining: + in pleomorphic adenoma

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**DDx of adenoid cystic carcinoma**

- **Poorly differentiated/solid type**
  - basal cell adenoma
  - small cell carcinoma
  - poorly differentiated adenocarcinoma
  - undifferentiated carcinoma

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**Tumors with “basaloid” features**

- Pleomorphic adenoma
- Adenoid cystic carcinoma
- Basal cell adenoma
- PLGA
- Basaloid squamous cell CA

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**Acinic cell carcinoma**

- Rare, accounting for about 1% of all salivary gland neoplasms
- But is 2nd most common salivary gland malignancy in children (after mucoepidermoid CA)
- ~75% occur in the parotid
- Is the most common bilateral, malignant primary salivary gland tumor
Warthin tumor

- Almost always near or in parotid gland, rarely in submandibular gland, almost never elsewhere
- Second most common benign salivary gland neoplasm, but accounts for only about 5-10% of cases
- Warthin tumor is the most common bilateral salivary gland neoplasm
  - 5-10% of salivary gland neoplasm are bilateral
  - 70% of those are Warthin tumours
- More common in men at 5:1
Warthin tumor-Pitfalls

• Can exhibit prominent squamous metaplasia
  – Can lead to misdiagnosis of squamous cell CA
• Other tumors exhibit oncocytic cells
  – Oncocytoma
  – Pleomorphic adenoma
  – Metastases

FNA cytology of salivary gland

• Sensitivity: 90%
• Specificity: 95%
• Diagnosis achieved in up to:
  – 90% of benign
  – 75% of malignant lesions
  – 60-80% for exact tumor subtyping

References


References