Thyroid Cytopathology

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Thyroid FNA Made Easy

- **Granulomatous Thyroiditis**
  Giant cells munching on colloid

- **Hashimoto Thyroiditis**
  Lymphocytes + Oncocytes

- **Papillary Carcinoma**
  Papillae, nuclei, cytoplasm

- **Medullary Carcinoma**
  Carcinoid + amyloid

- **Anaplastic Carcinoma**
  Ugly giant & spindle cells

- **Follicular Lesions?**
  Colloid vs Cells
Granulomatous Thyroiditis

See giant cells:
Think PTC!

Giant cells munch on yummy colloid

Epithelioid Histiocytes

Postviral syndrome; painful
Hashimoto Thyroiditis

Lymphocytes

Oncocytes

Clues: Infiltration; Tangles; Plasma cells; LGBs
Papillary Carcinoma

3 Best Clues
1. Papillae
2. Nuclear grooves or inclusions
3. Squamoid cytoplasm
Medullary Carcinoma
Carcinoid + Amyloid

ICC: Calcitonin

When you don’t know... think medullary carcinoma!
Anaplastic Carcinoma

Ugly Giant & Spindle Cells

“Ugly Cells”
Think Anaplastic CA, exclude metastasis
Follicular Lesions...

...the *problem* diagnosis
Follicular Lesions

- Goiter
  Nonneoplastic

- Follicular Neoplasms
  Adenoma
  Carcinoma

- Follicular Variant PTC
  All more/less encapsulated nodules of follicles
Goiter vs Neoplasm

~Never Follicular CA

Could be Follicular CA
This is so cool...

FNA biopsy can predict follicle size!
Micronodules
Clues to Diagnosis

More *colloid*

...more likely *benign*

More *cells*

...more likely *neoplastic*
Colloid vs Cells

Zone I
Colloid Nodule (BTN)
Very low risk of malignancy

Zone II
Cellular Nodule (FLUS)

Zone III
Follicular Nodule (SFN)
15%-30% risk of malignancy

Colloid Cellular Follicular Nodule Nodule Nodule (BTN) (FLUS) (SFN)
3 Steps: Follicular Lesion Dx

1. Colloid vs Cells
2. Refine distinction
3. Exclude Papillary CA
1. Colloid vs Cells*

Zone I: Colloid nodule
   Colloid >> Cells

Zone II: Cellular nodule
   Colloid ≈ Cells

Zone III: Follicular nodule
   Cells >> Colloid

*LBC concentrates cells, loses colloid*
Colloid

Watery Colloid

Dense Colloid
Fun with colloid
2. Refine distinction

- Clues to goiter
- Clues to neoplasm
- Clues to carcinoma
Clues to Goiter

- Fewer cells, more colloid
- Degeneration, Regeneration
  - Hemorrhage, Fibrosis, Cysts (foam cells, macrophages, cholesterol), Calcification
  - Atypical epithelium (WARD cells)
- Variable cells and cell types
- Wide range follicle size
- Honeycomb sheets
Honeycomb

=> Macrofollicles
Hemorrhage
Cystic Degeneration

“Nondiagnostic: cyst content”
Perifollicular Fibrosis
Calcification
Paravacuolar Granules

Hemosiderin, Lipofuscin
Flame Cells, Hurthle Cells, etc

Flame Cells
Repair/Degeneration: Atypical Epithelium

WARD Cells:
Worrisome Atypia in Reactive/Degenerative Cells

WARD Cells often Line Cysts
Clues to Neoplasm

High cellularity/scant colloid

Microfollicular pattern

Nuclei: Uniform, ± enlarged

Chromatin: May be coarse

Nucleoli infrequent

Atypical epithelium (WARD cells)

usually correlates with goiter!
Clues to Neoplasm

Microfollicles
Follicular Lesions

Colloid
Honeycomb

Zone I
BTN

Zone II
FLUS

Zone III
SFN

Cells
Microfollicles
Clues to Follicular CA

Marked...

Architectural Abnormality
- Crowded, 3D groups
- Irregular microfollicles
- Increased single cells

Cytologic Atypia
- Nuclear Enlargement
- Pleomorphism
- Abnormal chromatin
- Prominent or multiple nucleoli
- Mitosis (atypical); Necrosis

Increases risk of malignancy!
Follicular Carcinoma

Distorted Follicles

Cytologic Atypia

Atypia correlates with invasion!
Follicular Carcinoma

Two Forms...

- Minimally invasive
  - Minimally atypical
    - Minimally malignant

- Frankly invasive
  - Frankly atypical
    - Frankly malignant
3. Exclude Papillary CA

No matter what zone,

look at nuclei to exclude PTC

(colloid is irrelevant!)
Follicular Variant PTC

Nuclear features key:

- Nuclear grooves (extensive)
- Intranuclear Inclusions (even 1)

Other: Powdery chromatin, Marginated nucleoli, Papillae, squamoid cytoplasm, psammoma bodies, etc

Oranges vs Potatoes
Intranuclear Cytoplasmic Invaginations

NOT Orphan Annie Eyes!
Intranuclear Cytoplasmic Invaginations (INCIs)

99/100 Malignant; 9/10 PTC

Fewer INCIs, stricter criteria

If debatable: Not diagnostic

Often cluster, but if numerous, probably bubble artifact

Search-> epiphany: Zen of Cytology
A confusion of tongues...

The Bethesda System
# Report Format: 6 Tiered System

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cancer Risk</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Nondiagnostic</td>
<td>NA</td>
<td>Rpt w/ US</td>
</tr>
<tr>
<td>II. Benign</td>
<td>&lt;3%</td>
<td>F-U Clinically</td>
</tr>
<tr>
<td>III. AUS ACUS, FLUS</td>
<td>5%-15%</td>
<td>Rpt FNA</td>
</tr>
<tr>
<td>IV. Follicular Neoplasm*</td>
<td>20%-30%</td>
<td>Surgery</td>
</tr>
<tr>
<td>V. Suspicious</td>
<td>60%-75%</td>
<td>Surgery</td>
</tr>
<tr>
<td>VI. Malignant</td>
<td>97%-99%</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

*Specify if Hürthle Cell type*
I. Non-Diagnostic

Limited cellularity
Poor fixation
Excess blood
Poor cell preservation
Adequacy

6 groups of $\geq 10$ well prepared, well visualized follicular cells

Exceptions:
- Thick colloid (Benign)
- Thyroiditis (Benign)
- Any atypia
II. Benign

**Colloid nodular disease**
- Colloid nodule
- Hyperplastic/adenomatomoid nodule
- Macrofollicular adenoma

**Thyroiditis**
- Acute thyroiditis
- Hashimoto thyroiditis
III. Atypia of Undetermined Significance (AUS)

Atypical Cells of Undetermined Significance (ACUS)

Follicular Lesion of Undetermined Significance (FLUS)

Not convincingly benign, but not sufficient for more definitive dx

Risk malignancy 5% to 15%
AUS: Diagnostic Uncertainty

Microfollicles, Hürthle cells, cyst lining cells, or focal features of PTC

Eg, prominent microfollicles or Hürthle cells, but low overall cellularity

Compromised specimens common eg, low cellularity, poor fixation, obscuring blood, excessive clotting
AUS due to poor fixation

R/O Papillary Carcinoma
IV. (Suspicious for) **Follicular Neoplasm***

*Specify if Hürthle cell type

Follicular patterned lesions *lacking* nuclear features of PTC

Risk malignancy 15% to 30%

Notes:

1. Up to 35% non-neoplastic
2. Of malignancies, up to 68% = PTC
V. Suspicious for Malignancy

Suspicious for specific cancer, eg, PTC
Patchy/incomplete nuclear features
Suspicious due to lesion necrosis, eg, ATC
Risk malignancy 60% to 75%
VI. Malignant

Diagnostic of malignancy
Specify type if possible
Risk malignancy 97%-99%
You’ve got cancer !!!
Thyroid Cancer

5th most common cancer in women
True increase?

1. Environmental carcinogens
2. Environmental radiation
3. Other factors, eg, iodine?
Or something else?

1. Advances in diagnostic imaging
   Detects more abnormalities

2. Increased histologic sectioning
   Detects incidental micro PTCs
   Detects more invasion (FAd→FCA)

3. More liberal diagnostic criteria
   Increased diagnosis of cancer
You’ve got cancer!!!

*Up to 100% of adults have thyroid “cancer”*

Harach HR et al:
Occult Papillary Carcinoma of the Thyroid

*Cancer* 56: 531-538, 1985
You’ve got cancer!!!

*Up to 100% of adults have thyroid “cancer”*

Thank you
Advanced Thyroid Cytology

Hürthle cell lesions
Poorly differentiated carcinoma
Hyalinizing trabecular neoplasms
Hematologic malignancies
Metastases
Graves disease
Therapeutic effects
Dyshormonogenetic goiter
Pregnancy
The Bethesda System
Hürthle Cell Lesions

Can of Worms?
Mixed Bag of Lesions

Metaplastic Change

- Goiters
- Thyroiditis
- Adenomas
- Carcinomas
## Guidelines

<table>
<thead>
<tr>
<th>Favors benign or nonneoplastic</th>
<th>Favors neoplastic or malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloid</td>
<td>Diffuse atypia</td>
</tr>
<tr>
<td>Honeycomb sheets</td>
<td>Microfollicles</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>High N/C ratios</td>
</tr>
<tr>
<td></td>
<td>PTC features</td>
</tr>
</tbody>
</table>
Cutting the Gordian Knot

If exclusively Hürthle cells:

~75% chance neoplastic
If neoplastic, ~33% malignant
=> ~1 in 4 chance of cancer

Dx: (Suspicious for)
Hürthle cell neoplasm

Recommend: surgery
Poorly Differentiated Carcinoma

Insular and Non-Insular types

1. Solid/trabecular/insular growth
2. No PTC nuclear features
3. At least one of:
   a. Convoluted nuclei
   b. ↑ Mitotic activity
   c. Necrosis

TG, TTF-1 (+); Calcitonin (−)
Hyalinizing Trabecular Neoplasms

Unique entity vs PTC vs Others?
Nuclei: Similar to PTC
Cytoplasm: No NSGs
Background: ± Psammomas
DDx: PTC, Medullary CA
Thyroglobulin (+), Calcitonin (−)
Hematologic Malignancies

- Sudden growth in Hashimoto thyroiditis
  - Diffuse large B cell (easier to dx)
  - MALTomas (harder to dx)
  - Other lymphomas rare

DDx: Florid lymphoid phase Hashimoto
TGFF: Thank god for flow (cytometry)
Thyroid Sarcomas

Primary sarcomas:
Extremely rare

Examples: Lipo-, leiomyo-, angio- sarcoma

DDx: Most “sarcomas” = anaplastic CA*

*Both TG and CK can be (−) in anaplastic CA
Metastases

Not rare, but rarely dx in past
FNA Bx → antemortem dx
Most pts have known history
Grave prognostic sign
Often PD, unlike most 1°’s
Kidney, lung, breast, GI;
melanoma; lymphoma
Graves Disease

Related to Hashimoto Disease

Clinical and lab findings

FNA biopsy:
- High cellularity
- Pale watery colloid
- Flame and Hürthle cells
- Inflammation, granulomas
Therapeutic Effects

Radiation or antithyroid Rx
→ marked cytologic atypia

Pearl: Random atypia, mitoses rare

Radiation: ↑ risk CA, esp PTC
Dyshormonogenetic Goiter

Congenital hypothyroidism
Autosomal recessive
Enzyme defects in hormone synthesis → goiter
FNA: High cellularity, atypical cells, microfollicles, scant colloid
Mimics neoplasm, may favor CA
Actual malignant change rare!
Pregnancy

Iodine lost in urine
  → thyroid hyperplasia

FNA Biopsy:
  High cellularity, watery colloid, flame cells

Papillary hyperplasia may suggest PTC

Women of childbearing age at risk of PTC

Look for usual features of PTC to dx:
  Nuclear grooves, INCIs, etc, etc
Mission:
IMPOSSIBLE?
Things are not what they seem...

The blind and the elephant
Seems Malignant = Benign!

Atypical Adenoma
Seems Benign = Malignant !!

Well Differentiated Follicular Carcinoma
Non-neoplastic !!!

Goiter (Dyshormonogenetic)

Hashimoto Thyroiditis

Radioiodine Rx

Antithyroid Rx
Histologic Diagnosis

Can be difficult & subjective

- Capsular invasion vs trapped glands
- Vascular invasion not always easy dx
- Wide invasion vs some other tumor eg, insular carcinoma
- Metastasis vs sequestered goitrous nodule vs lateral aberrant thyroid
- Follicular variant PTC: most common
Gold Standard Failure

Up to 3/4 of follicular carcinomas histologically misdiagnosed*

*“interobserver variation”
Conclusion

Differential diagnosis
- Nonneoplastic nodules
- Follicular adenomas
- Carcinomas

...is impossible