Thyroid Cytopathology

Richard M. DeMay, MD
Professor of Pathology
Director of Cytopathology
The University of Chicago

Diseases of the Thyroid

1. Thyroiditis
2. Follicular lesions
   Goiters
   Neoplasms
3. Other thyroid neoplasms
4. Advanced topics

Granulomatous Thyroiditis

Postviral (cold, flu) syndrome
Painful thyroid; fever, chills, fatigue

Epithelioid Histiocytes
Multinucleated Giant Cells
Giant cells munch on yummy colloid
See giant cells: Think papillary carcinoma!

Granulomatous Reactions

Nonneoplastic goiter
Hashimoto thyroiditis
Granulomatous thyroiditis
Systemic granulomatous ds, eg, sarcoidosis
Specific infections, eg, TB, fungal
Palpation thyroiditis
Previous FNA biopsy
Foreign body reactions, eg, to Teflon, suture
Malakoplakia
Reaction to tumors, eg, papillary CA

Hashimoto Thyroiditis

Classic autoimmune disease
Mid-age, white F (typical)
Diffuse goiter, hypothyroidism
+ Antithyroid antibodies
Dx: Lymphocytes + oncocytes form spectrum
DDx: Lymphoma vs Hürthle cell neoplasm

Hashimoto Thyroiditis

Lymphocytes
Oncocytes
Colloid usually scant
4 Clues to Chronic Inflammation

- Plasma Cells
- Lymphoid Tangles
- Lymphoglandular Bodies
- Lymphs → Epithelium

Papillary Carcinoma

75-80% of thyroid cancers
Any age, mean = 45 yrs
Bimodal 25-30, 55-60
F > M (2-4 x)
Prognosis usually excellent
Except: older age, male, large (>4cm), distant mets, recurrence, aggressive types, eg, tall cell

FNA Bx: Papillary Carcinoma

Architecture
1. 3D papillae w/ cores
2. 3D “caps” w/o cores
3. Monolayered sheets
4. “Swirls”

Cytoplasm
5. Squamoid
6. Septate vacuoles

Nuclei
7. Grooves
8. INClS
9. Fine, pale chromatin
10. Marginated nucleoli

Background
11. Psammoma bodies
12. Epithelioid giant cells
13. Gummy colloid

3 Best Clues
1. Papillae
2. Nuclear grooves or inclusions
3. Squamoid cytoplasm

Variants of Papillary Carcinoma

- Follicular
- Macrofollicular
- Encapsulated
- Hürthle cell (oncocytic)
- Warthin-like
- Diffuse sclerosing
- Tall cell
- Columnar cell
- Solid
- Cribriform-morular
- Dedifferentiated
- Also: microcarcinoma

Some Variants of PTC

- Follicular
- Hürthle
- Tall Cell
- Adenoid cystic
- Cribriform
- Morular
**Poorly Differentiated Carcinoma**
Insular and Non-Insular types
1. Solid/trabecular/insular growth patterns
2. No PTC nuclear features
3. At least one of:
   a. Convoluted nuclei
   b. ↑ Mitotic activity
   c. Necrosis
TG, TTF-1 (+); Calcitonin (–)

**Anaplastic Carcinoma**
Recent rapid growth in long standing nodule in elderly patient
"Ugly Cells"
Think Anaplastic CA, exclude metastasis

**Medullary Carcinoma**
Malignant tumor with C cell neuroendocrine differentiation
Thyroid nodule + ↑ serum calcitonin
- 75% sporadic: solitary nodule
- 25% familial: bilateral, younger pt
Associated with RET mutations
"The Great Mimicker"
Follicular, Follicular/parafollicular, Oncocytic (Hürthle cell), Clear cell, Papillary, Small cell, Spindle cell, Giant cell (anaplastic) variants

**Medullary Carcinoma**
Carcinoid + Amyloid
Lymphoplasmacytoid
Spindle
Anaplastic

**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!

Macronodules

Micronodules

Clues to Diagnosis

More colloid
...more likely benign

More cells
...more likely neoplastic

Colloid vs Cells

Colloid
Very low risk of malignancy

Zone I

Zone II

Zone III

Benign Thyroid Nodule
Follicular Nodule of Undetermined Significance
Follicular Neoplasm
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

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

2. Refine distinction

- Clues to goiter
- Clues to neoplasm
- Clues to carcinoma
Honeycomb

=> Macrofollicles

Cystic Degeneration

“Nondiagnostic: cyst content”

Perifollicular Fibrosis

Hemorrhage

Stromal Fibrosis

Calcification
**Paravacuolar Granules**

Hemosiderin, Lipofuscin

**Flame Cells, Hurthle Cells, etc**

Flame Cells

**Range of Follicle Size**

**WARD Cells: Atypical Epithelium**

WARD Cells:
- Worrisome Atypia in Reactive/Degenerative 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

- Zone I: BTN
- Zone II: FLUS
- Zone III: SFN

- Colloid: Honeycomb
- Cells: Microfollicles

Clues to Follicular CA

Marked...
- Architectural Abnormality
  - Crowded, 3D groups
  - Irregular microfollicles
  - Increased single cells
- Cytologic Atypia
  - Nuclear Enlargement
  - Pneumophils
  - Abnormal chromatin
  - Prominent or multiple nucleoli
  - Mitosis (atypical); Necrosis

Increases risk of malignancy!

Follicular Carcinoma

Two Forms...
- Minimally invasive
  - Minimally atypical
    - Minimally malignant
- Frankly invasive
  - Frankly atypical
    - Frankly malignant

Cytologic Atypia

Atypia correlates with invasion!

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

3. Exclude Papillary CA

No matter what zone,
look at nuclei to exclude PTC
(colloid is irrelevant!)
Intranuclear Cytoplasmic Invaginations (INCI)

99/100 Malignant; 9/10 PTC

Fewer INCI, stricter criteria
If debatable: Not diagnostic
Often cluster, but if numerous, probably bubble artifact
Search→epiphany: Zen of Cytology

Advanced Thyroid Cytology

Hürthle cell lesions
Riedel thyroiditis
Poorly differentiated carcinoma
Hyalinizing trabecular neoplasms
Hematologic malignancies
Metastases
Graves disease
Therapeutic effects
Dyshormonogenetic goiter
Pregnancy

Hürthle Cell Lesions

Mixed Bag of Lesions

Metaplastic Change
- Normal (↑ age)
- Goiters
- Thyroiditis
- Adenomas
- Carcinomas

Favors Nonneoplastic
Colloid, Inflammation
Honeycomb Sheets

Favors Neoplastic
Microfollicles, Diffuse atypia,
High N/C, PTC features
**Hürthle Cell Nodules**

*Cutting the Gordian Knot*

- Nearly exclusively Hürthle cells
- 75% chance neoplastic
- 33% malignant if neoplastic
- 25% overall malignant risk

Dx: Suspicious for Hürthle cell neoplasm

Recommend surgery

**Hyalinizing Trabecular Neoplasms**

- Unique entity vs PTC vs Others?
- Nuclei: Like PTC, numerous INCIs
- Cytoplasm: Hyaline bodies, no NSGs
- Bkgrnd: Hyaline material, ± Psammomas
- Dkx: PTC, Medullary CA
- Thyroglobulin (+), Calcitonin (–)

**Riedel Thyroiditis**

- Reactive spindle cells
- Myofibroblast

Very rare, F:M
- IgG4 sclerosing dx, EBV?
- Painless, nontender
- Woody hard, infiltrative
- FNA Bx: Scant, unsat?
- DDKx: Fibrosing Hashimoto
- Hypothyroid, ↑↑↑ autoAbs

**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
  - Liposarcoma
  - Leiomyosarcoma
  - Angiosarcoma

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 1st s
- Kidney, lung, breast, GI; melanoma; lymphoma

DDx: Primary thyroid lesion

**Kidney**

- Lung
Graves Disease

Autoimmune disease related to Hashimoto thyroiditis
Dx: Clinical and lab findings
FNA biopsy:
  High cellularity
  Pale watery colloid
  Flame and Hürthle cells
  Inflammation, granulomas
± Therapy atypia

Therapeutic Effects

Radiation or antithyroid Rx
→ marked cytologic atypia
Pearl: Random atypia, degeneration
Clinical history crucial in diagnosis!

Dyshormonogenetic Goiter

Congenital hypothyroidism
Autosomal recessive
Enzyme defects in hormone synthesis → goiter
FNA: High cellularity, atypia, 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

Molecular Diagnosis

<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>PTC</th>
<th>FTC</th>
<th>PDTC</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS</td>
<td>15%</td>
<td>45%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>BRAF</td>
<td>50%</td>
<td>0</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>RET/PTC</td>
<td>33%</td>
<td>0</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>PAX8/PPARγ</td>
<td>&lt;5% (FVPTC)</td>
<td>50%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>β53</td>
<td>&lt;5%</td>
<td>5%</td>
<td>25%</td>
<td>70%</td>
</tr>
<tr>
<td>β-catenin</td>
<td>0</td>
<td>0</td>
<td>25%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Final Thoughts

FNA Bx of a thyroid nodule is benign ...
... until proven otherwise!
Most thyroid nodules, by far, are benign
Most are benign colloid nodules
Most can be diagnosed by cytology
Most malignant nodules, by far, are PTCs
Most PTCs can be diagnosed by cytology
Therefore:

As a first approximation:
FNA biopsy of thyroid is either
Papillary Carcinoma* or Benign**

*Or other easily recognized cancer
**Most follicular lesions are benign
(goiter, thyroiditis, adenomas: FTC is rare)

The Bethesda System

Indications for FNA biopsy
Pre-FNA requirements
Training/credentialing
Techniques for FNA biopsy
Specimen adequacy
Diagnostic terminology
Ancillary studies
Post-FNA testing/treatment

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>Follow Clinically</td>
</tr>
<tr>
<td>III. AUS</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

Sparse or degenerated cells
Cyst content (no epithelial cells)
Other (eg, obscured, clotted)

Adequacy

6 groups of ≥10 well prepared, well visualized follicular cells

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

Colloid nodular disease
  Colloid nodule
  Hyperplastic adenomatoid nodule
  Macrofollicular adenoma
Thyroiditis
  Acute thyroiditis
  Hashimoto thyroiditis

III. Atypia of Undetermined Significance (AUS)

Atypical Cells of Undetermined Significance (ACUS) Cytologic atypia
Follicular Lesion of Undetermined Significance (FLUS) Architectural atypia
Not convincingly benign, but not sufficient for more definitive diagnosis
Risk malignancy: 5% to 15%

AUS: Diagnostic Uncertainty

Microfollicles, Hürthle cells, cyst lining cells, Rx atypia, 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 Epidemic

True increase?
1. Environmental carcinogens
2. Environmental radiation
3. Other factors, e.g., obesity

Bottled Water Consumption

Plastics have estrogen-like compounds; may disrupt thyroid endocrine function
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:
A ‘Normal’ Finding in Finland.
Cancer 56: 531-538, 1985

Thank you

All images copyright ASCP Press