Challenging Cases in Thyroid Cytopathology

OBJECTIVES

Discuss and correlate ultrasound features of thyroid lesions with FNA cytology

Discuss changes and new additions to the upcoming second edition of TBSRTC

Normal Anatomy
Thyroid
The Bethesda System for Reporting Thyroid Cytopathology

Recommended Diagnostic Categories

I. Nondiagnostic or Unsatisfactory
   A. Poorly defined
      - Virtually acellular specimen
      - Other (observing blood, clumping artifact, etc)

II. Benign (RISK 0-3%)
   Consistent with a benign follicular nodule
   (includes adenomatoid nodule, colloid nodule, etc)
   "Diagnostic":
   Lymphocytic (Hashimoto) thyroiditis in the proper clinical context
   Other: granulomatous (subacute) thyroiditis, Graves', acute thyroiditis, Reidel thyroiditis

III. Atypia of Undetermined Significance or FLUS
   (RISK 5-15%)

IV. Follicular Neoplasm or Suspicious for a FN
   Specify if Hürthle cell (oncocytic) type
   (RISK 15-30%)

V. Suspicious for Malignancy
   (RISK 60-75%)
   Suspicious for papillary carcinoma
   Suspicious for medullary carcinoma
   Suspicious for metastatic carcinoma
   Suspicious for lymphoma
   Other

VI. Malignant (RISK 97-99%)
   "Diagnostic":
   Papillary thyroid carcinoma
   Poorly differentiated carcinoma
   Medullary thyroid carcinoma
   Undifferentiated (anaplastic) carcinoma
   Squamous cell carcinoma
   Carcinomas with mixed features (specify)
   Metastatic carcinoma
   Non-Hodgkin lymphoma
   Other
Screening
- Follicular Lesions
  - Multinodular Goiter
  - Follicular Adenoma
  - Follicular Carcinoma

Majority of follicular lesions will be benign

<table>
<thead>
<tr>
<th>AUS/FLUS/</th>
<th>Suspicious</th>
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<tbody>
<tr>
<td>Cytologic and architectural atypia</td>
<td>Microfollicles and/or crowded groups</td>
</tr>
<tr>
<td>Limited cellularity</td>
<td>Increasing cellularity</td>
</tr>
<tr>
<td>Preparation artifact</td>
<td>Decreasing colloid</td>
</tr>
<tr>
<td>Micronodules w/macro</td>
<td>Cytologic atypia (nuclear)</td>
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<tr>
<td>Atypia not quite suspicious</td>
<td>Entropod</td>
</tr>
<tr>
<td>for PTC</td>
<td>Clumped chromatin</td>
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<tr>
<td></td>
<td>Nuclear</td>
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<tr>
<td>Repeat FNA ~ 50% will be reclassified as</td>
<td>Grooves</td>
</tr>
<tr>
<td>benign</td>
<td>NIFTP, FVPTC, or PTC</td>
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</table>

TBSRTC II

Group Leaders for the Yokohama meeting:
Bill Faquin, Marc Pusztaszeri; Esther Diana Rossi

- Pubmed literature review of thyroid cytology from 2010 to present
- Divided efforts into subgroups corresponding to each of the 6 TBSRTC diagnostic categories: 2-6 panel members per subgroup
- Email discussions among subgroup members, and face to face meeting at USCAP in Seattle. IAC Symposium presentation – Yokohama, Japan
- Publication of manuscript detailing the panel’s consensus recommendations for TBSRTC II
Cystic lesions:
Should still be reported as Non-diagnostic with an explanatory note. Update management according to revised ATA guidelines. The sample reports and the explanatory notes in TBSRTC regarding cystic lesions are adequate.

Repeat FNA after ND result:
The wait time for repeating an FNA after a ND result can be less than 3 months (as suggested by the revised ATA guidelines). However, it should be explained that reactive atypia and cellular changes may be present if the delay to repeat FNA is shortened.

Adequacy criteria and preparation method:
Clarification is needed pertaining to the specific adequacy criteria for smears vs. liquid based preparations: ThinPrep and Surepath alone or in combination with smears.

The Future of Adequacy

63 year old woman—recent dx of FOM SCCa; thyroid nodules noticed on CT

4.2 x 2.8 x 1.3 cm
Round, cystic nodule
Well-defined borders
Hypoechoic
No vascularity in lesion but peripheral vascularity

Smaller nodules with identical features are seen in the left thyroid.

FNA Cytology:
Cell block shows rare macrophages in a background of bland, noncohesive
No follicular
Diagnosis
Benign c/w Simple cyst
Non-Diagnostic

Right Lobe Thyroid:
2.7 cm
Heterogeneous echo pattern
Smooth borders
No calcifications
Avascular (Doppler)

FNADx: Non-malignant thyroid nodule with cystic degeneration

56 year old man noted a swelling in the right side of his neck while shaving. He denies any trauma, pain, fever, chills or night sweats.
What is the best interpretation for this thyroid US?

Hemorrhagic cyst
Cystic degeneration
Follicular tumor with cystic change
Cystic papillary carcinoma

Left Lobe Thyroid:
3.2 x 3.1 x 2.8 cm
Complex nodule
Hypoechoic
Nonhomogeneous echo pattern
Smooth margins
No calcifications
Posterior enhancement
Avascular (Doppler)

FNA Cytology:
Blood and hemosiderin laden macrophages
Diagnosis:
Hemorrhagic cyst
Non-Diagnostic

Right Lobe Thyroid:
4.9 x 4.7 x 2.7 cm
Anechoic cyst w/ isoechoic solid areas
Well defined borders
No calcifications
Avascular (Doppler)

US impression:
Complex colloid cyst with an echogenic mural nodule, possible hematoma that has increased in size since a previous study

FNA Cytology:
The aspirate shows abundant blood with hemosiderin laden macrophages, evidence of cystic degeneration or acute hemorrhage

Diagnosis:
Hemorrhagic cyst
Non-Diagnostic

52 year old woman with a right thyroid nodule x years.
FNA 2 years ago was benign, mass increased in size.
Recommendation 10
Non Diagnostic Cytology

Definition: 6 groups of well visualize follicular cells; each group containing at least 10 follicular cells on 2 slides

NonDx- repeat with USFNA and if available ROSE
Repeatedly NonDx samples:
close watch or excision for nodules without high suspicion sonographic pattern
excision for nodules with high suspicion sonographic pattern; growth of nodules (>20%), or if clinical risk factors exist

Repeat FNA using USFNA increases adequacy rate
(DON'T need to wait 3 months post initial FNA to avoid FP Dx due to reactive atypia) Most are benign.

Cystic Lesions in Thyroid
- Multinodular goiter
- Hemorrhagic cyst
- Thyroiditis
- Cystic degeneration in follicular tumors
- Papillary carcinoma
- Thyroglossal duct cyst

Well defined
Unilocular, although may have septations
Echogenic debris (comet tails, metazoa, Ca++)
Solid areas
may be blood products of varying age
may be malignant (PTC)
Occasional history “rapidly enlarging”

47 year old woman- Hx of IVDU, hepatitis C, on IV antibiotics for a cavitary lung lesion now has incidental bilateral thyroid nodules seen on chest CT scan.

Left Thyroid: Bilobed? rounded, solid hyperechoic nodule that measures 2.4 x 1.7 cm, no calcifications, avascular

Right Thyroid: Heterogeneous lobe with an ill defined 1.2 x 0.8 cm area with hypochogenic features, avascular.

Benign Normal
A “nodule” may be a nodule or may be the expression of limited ultrasound imaging!
What does the image at the arrows represent in this thyroid US?

Small blood vessel
Fascia of strap muscle
Egg shell calcifications
Capsule of thyroid nodule

Answer: Egg shell calcifications

Egg shell calcification with peripheral vascularity.
An unbroken rim favors a benign nodule.
A disrupted rim is more worrisome for malignancy.

"In conclusion, in thyroid nodules with eggshell calcifications and no other calcifications, the findings of a peripheral halo and disruption of eggshell calcifications may be more useful sonographic predictors of malignancy than the sonographic features of hypoechogenicity, microlobulated margins, and a taller-than-wide shape."
Comet Tails!
- Echogenic foci without posterior shadowing
- Suspended aggregates of colloid
- Typically seen in colloid cysts, non-neoplastic nodules with cystic degeneration and/or hemorrhagic cysts
- Mimic punctate calcifications of malignant thyroid tumors (PTC, Medullary Ca)

Microcalcifications
- Coarse calcifications are commonly identified in multinodular goiters (dystrophic Ca++)
- More worrisome if present in a solitary nodule—increased risk of malignancy

Posterior shadowing: when ultrasound hits a calcification and is completely reflected such that a shadow is formed.

Coarse calcifications
- Markedly hypoechoic
- Solid consistency
- Irregular, infiltrating margins
- Increased vascularity

Microcalcifications
- Hypervascularity

US Criteria for Benign vs Malignant

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
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<tbody>
<tr>
<td>Entirely cystic (anechoic)</td>
<td>Microcalcifications</td>
</tr>
<tr>
<td>Nearly cystic</td>
<td>posterior shadowing</td>
</tr>
<tr>
<td>no vascularity</td>
<td>Markedly hypoechoic</td>
</tr>
<tr>
<td>no Ca++</td>
<td>solid consistency</td>
</tr>
<tr>
<td>Spongiform pattern</td>
<td>Irregular, infiltrating margins</td>
</tr>
<tr>
<td>no Ca++</td>
<td>Increased vascularity</td>
</tr>
<tr>
<td>“Hash” pattern</td>
<td></td>
</tr>
<tr>
<td>hypervascularity</td>
<td></td>
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</table>
Nodules that are most likely benign

- Anechoic cysts
- Nodule < 2 cm that is almost entirely cystic with no intranodal vascularity or calcifications
- Nodule < 2 cm that is spongiform without Ca++
- “Pseudonodules” in Hashimoto thyroiditis (also Graves dr)
- Mixed solid and cystic nodules with functioning solid component (‘hot’ nodule)
60 year old woman with primary hyperparathyroidism. She has long standing hypothyroidism – etiology- on Synthroid.

FNA Dx:
BENIGN/Thyroiditis
Thyroid follicular cells with oncocytic cell change and associated lymphoid tangles, consistent with a nodule of Chronic Lymphocytic (Hashimoto’s) Thyroiditis

Hashimoto’s Thyroiditis
US features will vary with stage of disease

**Acute**
- Focal
  - discrete nodules in equal frequency against normal background
- Diffuse
  - entire gland shows enlarged, hypoechoic, heterogeneous micronodular echo pattern
- Doppler
  - variable vascularity; focal nodules may mimic benign or malignant nodule

**Chronic**
- Diffuse
  - enlarged, hypoechoic, micronodular gland with echogenic parenchymal echoes, echogenic (pink) fibrous septae
- Doppler
  - hypervascular when pt. is euthyroid
- Atrophic
  - small hypoechogenic gland with heterogeneous echo pattern
Ask non-directed clinical questions related to:

- Fatigue
- Hair loss
- Weight issues
- Emotional lability

Enlarged gland, diffuse process “Moth eaten” thyroid, heterogeneous echo pattern with hypervascularity

61 y.o. woman with multinodular thyroid and a family history of thyroid carcinoma. She had 4 nodules with three on the right (one posterior subcentimeter nodule on the left) all sonographically similar.
Nodule #1 and #3
Nodule #2
Nodule #2
Benign
Nodules #1 and #3

6 month follow-up. Multinodular right lobe nodules essentially unchanged. AUS Nodule #2 sampled. New Dx: Benign

DDX AUS / FLUS
- Hyperplastic nodule in nodular goiter
- Hyperplasia (Graves’ disease)
- Hurthle cell nodule in Hashimoto thyroiditis
- Follicular adenoma
- Follicular carcinoma, well differentiated
- Noninvasive follicular tumor with papillary like features (NIFTP)
- Papillary carcinoma, follicular variant
51 y.o. woman with 1.5cm right lobe nodule
Cyto Interpretation: AUS, favor benign

36 y.o. woman with 4cm nodule in the left lobe
Cyto Interpretation: AUS, favor FN

16 y.o. woman with 4cm nodule in the left lobe
Cyto Interpretation: AUS, favor FN
Take Home Points

AUS - if possible get consensus. Remember degenerative/cystic change is not AUS and endocrine atypia is not AUS. AUS is regarded as indeterminate and has a 5-15% risk of malignancy.

Use ATA guidelines when multiple nodules are identified. (Recommendation #8)
Repeat FNA, esp USFNA will exclude approx 50% of this category. Review prior material and images prior to repeat FNA.

Microfollicles are very strong indicators of a follicular lesion - but must be distinguished from spherules and benign follicles.

Follicular variant of PTC is difficult. Nuclear (INCI) features are not often present. Look for hard colloid. Think about NIFTP!

AUS/FLUS

Only one term should be selected by laboratory.

Repeat FNA:
- Is a suitable follow-up option in ATA 2015
- Limited cellularity contributes to the initial AUS/FLUS interpretation
- Compromised samples lacking atypia classify as Non Diagnostic
- Need clinical correlation (US findings, TSH antibody titre correlation, etc.)

Surgery:
- Generally discouraged for initial AUS/FLUS
- Reasonable option for second AUS

Molecular testing:
- Acceptable consideration for AUS/FLUS
- Reflexive molecular testing is not mandated for all AUS/FLUS

RECOMMENDATION 8:

Diagnostic FNA is recommended for:
- Nodules ≥ 1 cm in greatest dimension with high suspicion US pattern.
- Nodules ≥ 1 cm in greatest dimension with intermediate suspicion US pattern.
- Nodules ≥ 1.5 cm in greatest dimension with low suspicion US pattern.

Diagnostic FNA may be considered for:
- Nodules ≥ 2 cm in greatest dimension with very low suspicion US pattern (e.g., spongiform)
- Observation without FNA is also a reasonable option.

Diagnostic FNA is not required for:
- Nodules that do not meet the above criteria.
- Nodules that are purely cystic.

Patients with multiple thyroid nodules ≥1 cm should be evaluated in the same fashion as patients with a solitary nodule ≥1 cm excepting that each nodule that is >1 cm carries an independent risk of malignancy and therefore multiple nodules may require FNA. When multiple nodules ≥1 cm are present, FNA should be performed preferentially based upon nodule sonographic pattern and respective size cutoff. If none of the nodules has a high or moderate suspicion sonographic pattern, and multiple sonographically similar very low or low suspicion pattern nodules coalesce with no intervening normal parenchyma, the likelihood of malignancy is low and it is reasonable to aspirate the largest nodules (≥2 cm) or continue surveillance without FNA.

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. THYROID. Special Article 2016; 26(1):1-133

Pendred syndrome:
congenital, bilateral sensorineural hearing loss and goiter with euthyroid or mild hypothyroidism

21 year old woman with Pendred syndrome and bilateral thyroid nodules

Follicular neoplasm
55 year old woman noticed a left thyroid nodule 2 years ago. She presents with hoarseness and dysphagia.

9x6 cm nodule with lobulated contours, well-defined borders, heterogeneous with iso- and hypoechoic solid areas, scattered vascularity on Doppler.

FNA DX: Follicular Neoplasm

Hemithyroidectomy: Follicular Adenoma

48 year old woman with a thyroid nodule noted on routine physical. Referred to endocrinology. Asymptomatic.

Irregular margins
Calcifications
Invasion

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

THYROID. Special Article 2016; 26(1):1-133
Calcifications

“Invasion”

Papillary Thyroid Carcinoma

US Features: Papillary thyroid carcinoma

Solid (~70%), Hypoechoic (~77-90%), Multifocal (~10-20%)

Ill-defined, irregular outlines, may see incomplete lusos, disrupted borders

Doppler: chaotic vessels, esp. internal (intransmicrovascular)

“Punctate calcifications” very specific (may see posterior shadowing)

Disrupted rim calcifications with extrusion

12 year old girl with enlarged thyroid and neck lymph nodes
30 year old African American woman euthyroid with a left thyroid mass

2.9 x 2.0 x 1.5 cm mid left lobe complex, hypoechoic nodule with non-homogenous internal echo pattern. Margins are indistinct and jagged increased vascularity. Papillary Thyroid Carcinoma

50 year old woman with a history of multinodular goiter who now presents with a left superior thyroid nodule that is worrisome on radiology US scan. Endocrinology requested Pathology USFNA evaluation of this nodule.

FNA Diagnosis: Papillary Carcinoma
Final Dx:
Papillary Thyroid Carcinoma
Warthin-like variant

Take Home Points

Warthin-like PTC:
• Woman >50 years
• Clinical progression and prognosis similar to classical PTC
• May be seen in a background of chronic lymphocytic thyroiditis
• Cyto DxD: Benign LEL of thyroid
• Hurthle cell tumors
• Tall cell variant of PTC

42-year-old man status post allogeneic stem cell transplant (CML) complicated by pulmonary GVHD. Multiple symptomatic thyroid nodules originally found on physical exam six weeks earlier. Patient admits difficulty swallowing and coughing for the past year.
FNA Diagnosis: Papillary Carcinoma

Surgical Pathology DX:
- Thyroidectomy and Neck Dissection
- Right Lobe:
  - Papillary Carcinoma, Classic type
  - Papillary Carcinoma, Microcarcinoma
  - Hurthle Cell Carcinoma (Oncocytic)
- Left Lobe:
  - Non-invasive follicular tumor with papillary like features (NIFTP)
- Lymph Nodes, Right neck:
  - Metastatic PTC

Hurthle Cell Carcinoma
Follicular Neoplasm/Suspicious for Follicular Neoplasm (Hurthle Cell Type)
Hurthle cell vs Oncocytic. Oncocytic preferred (correlates with WHO terminology)

Do not be fooled by abundant colloid:
- A macrofollicular component is frequently present in oncocytic carcinoma, oncocytic adenoma and oncocytic adenomatoid nodules in nodular goitre. None of the cytological features studied (127 cases), including abundant colloid, can exclude oncocytic carcinoma. Oncocytic carcinoma can only be excluded by thorough histological examination of thyroidectomy specimens.

Yang GC, Schreiner AM, Sun W. Cytopathology, 2013 Jun;24(3):185-95

Non-invasive follicular tumor with papillary like features (NIFTP)
Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP)

Indolent behavior
Conservative Management (lobectomy without RI)

FNA: NIFTP has been classified using TBSRTC: AUS/FLUS; SFN/FN; SUS

Need histology for definitive Dx (similar to FN: is it FA or FC?)

Encapsulated/demarcated tumor with follicular growth pattern and nuclear features of PTC

Cytology
Micronodular pattern with mild nuclear changes (think FVPTC)
Can show INCh but uncommon
No papillary architecture
No psammoma bodies

Molecular
Mutations: RAS, BRAF K601E (not V600E)
Fusions: PPARG THADA

FVPTC is a PTC in which tumor is almost or completely composed of small (micro) to medium (normal) sized follicles lined by cells with nuclear features of PTC.

Most common variant (30%)
Presence of nuclear features is variable
Diagnostic: Suspicious for PTC
FN: Suspicious for FN

Papillary carcinoma, follicular variant

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30 year old woman with 2 left lobe nodules, one of which was calcified. Hypoechoic with ill defined borders.
Cyto interpretation: AUS.

46 year old woman with right lobe nodule, isoechoic and moveable.
Cyto interpretation: Suspicious for FVPTC.
Take Home Points

USFNAs
Multiple nodules on US
Patient with multiple nodules followed same as with one nodule
BUT each nodule carries independent risk of malignancy so a patient may need more than one FNA

FNA performed preferentially based on pattern and size
Ex: benign (anechoic cyst) no FNA vs low suspicion (FNA >2cm)
vs intermediate suspicion (FNA >1.5cm) vs high suspicion (FNA <1cm)

50% adults have thyroid nodules
Most subcentimeter- very low risk, no FNA needed
In practice most >1cm can be followed without FNA
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer


SPECIAL ARTICLE