Molecular Adjuncts to Cytologic and Histologic Diagnosis of Thyroid Nodules

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Disclosures

I have no financial support to disclose.

Incidence of Thyroid Nodules

- The reported incidence of thyroid nodules increases with age of patients and sensitivity of examination
- Population based studies show incidence in adults of 3.2-4.2% (Framingham Ma and Wickingham England)
- 50-65% of adults have thyroid nodules on autopsy
- Incidentally detected nodules found on MRI, CT for a variety of non thyroid related causes are evaluated
- Estimated 10 million adults have a thyroid nodule that could be aspirated

Incidentally Identified Thyroid Nodules

- Not evaluated for symptoms, cosmetic reasons, hyperfunction, respiratory compromise, or dysphagia
- Non palpable thyroid nodules of concern because of possible malignancy
- American Cancer Society 2013 statistics for thyroid cancer (all subtypes)
  - About 60,220 new cases of thyroid cancer (45,310 in women, and 14,910 in men)
  - About 1,850 deaths from thyroid cancer (1,040 women and 810 men)(www.cancer.org)

Which Nodules to Biopsy?

- Current threshold for biopsy is any nodule greater than 1 cm
- Based on presumed increase of morbidity in patients with nodules greater than 1.5 cm
- Smaller series found ~30% of non palpable nodules greater than 1 cm
- ~25% of patients with palpable nodule have a second nodule greater than 1 cm
- Recommended that no more than 4 nodules be biopsied.

How to Biopsy

Core biopsy

Fine needle aspiration

Bethesda Criteria

The Bethesda System for Reporting Thyroid Cytopathology

Edmund S. Cibas, MD, and Syed Z. Ali, MD

Am J Clin Pathol 2009;132:658-665

Diagnostic Criteria for Thyroid

- Inadequate/non diagnostic
- Benign
- Atypia of undetermined significance/follicular lesion of undetermined significance
- Suspicious for follicular neoplasm
- Suspicious for malignancy
- Malignant

Thyroid Diagnostic Categories

Diagnostic Category	Risk of Malignancy (%)	Usual Management
Non Diagnostic / Unsatisfactory	1-4%	Repeat FNA with ultrasound guidance
Benign	0-3%	Clinical Followup
Atypia of Undetermined Significance	~5-15%	Repeat FNA
Follicular Neoplasm	15-30%	Surgical lobectomy
Suspicious for Malignancy	60-75%	Near total thyroidectomy or surgical lobectomy
Malignant	97-99%	Near total thyroidectomy

The Bethesda System for Reporting Thyroid Cytopathology; *Am J Clin Pathol* 2009; 132:658-665

Non Diagnostic

- Non diagnostic aspirates include those with cyst fluid only (proteinaceous material and macrophages), cyst fluid or virtually acellular specimens, as well as those limited by obscuring blood, clotting artifact in which all of the cellular material is entrapped in clot.
- Adequacy is defined as 6 or more groups of 6-10 intact follicular cells. The original summation statement (Cytojournal 2008 5:6) recommended that these groups be on a single slide.

Colloid Nodules

“Any specimen that contains abundant colloid is considered adequate (and benign), even if 6 groups of follicular cells are not identified: A sparsely cellular specimen with abundant colloid is, by implication, a predominantly macrofollicular nodule and, therefore, almost certainly benign.”

“Specimens that consist only of cyst contents (macrophages) are problematic….At the 2007 NCI conference, it was decided that cyst-fluid-only (CFO) cases should be considered a clearly identified subset of ND/UNS.”

If repeat aspiration is non diagnostic, excision should be considered because some persistently non-diagnostic lesions are malignancy.

How Many Passes?

- With rapid onsite evaluation, and a standard protocol, our adequacy rate exceeds 95%.
- First pass – paired smears for alcohol fixation (later Pap stained) and air dried DiffQuik stain.
- Second pass, directly into RPMI or molecular diagnostic medium medium
- Third and fourth passes for paired smears

----------Evaluation----------

- Two more additional passes if needed

Exceptions To Adequacy Criteria

- Any sample that is diagnostic for another process, e.g. lymphocytic thyroiditis
- Samples with significant atypia/malignancy to warrant a diagnosis

Benign

- Most benign aspirates are hyperplastic nodules, nodular goiter, or follicular adenoma
- Benign follicular nodule
- Other benign diagnoses which may be included are lymphocytic thyroiditis or granulomatous thyroiditis

Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance

- Those with some groups with nuclear features worrisome for papillary carcinoma
- Cyst lining cells with atypia
- Therapy related epithelial changes
- Atypical lymphoid populations, suspicious for lymphoma
- Predominance of Hurthle cells without colloid
- Microfollicular populations without colloid not cellular enough for a diagnosis

Suspicious for Follicular Neoplasm

"The term *suspicious for a follicular neoplasm* is preferred by some laboratories over *follicular neoplasm.*"

The majority turnout to be follicular adenoma or hyperplastic nodules

Both follicular variant of papillary carcinoma and follicular carcinoma can appear as SFN on aspiration

Used for both a predominantly microfollicular or trabecular pattern without cytologic features of papillary carcinoma

Suspicious For Malignancy

- Nuclear changes of papillary thyroid carcinoma (ptc) can be focal
- Use for sparsely cellular samples
- If not all characteristics of ptc are not present
- Only a few groups have changes

Malignant

- Most are papillary carcinoma
- Metastases
- Medullary carcinoma
- Lymphoma
- Follicular carcinoma

- As pathologists, our aim is to refine criteria for biopsy and for ancillary techniques.
- The reported complication rates for FNA biopsy of the thyroid are low, but the complications include hemorrhage, some with respiratory compromise, infection, and unnecessary surgery.
- For follicular neoplasm through malignancy, the primary treatment is resection
- For atypia, the options are less clear

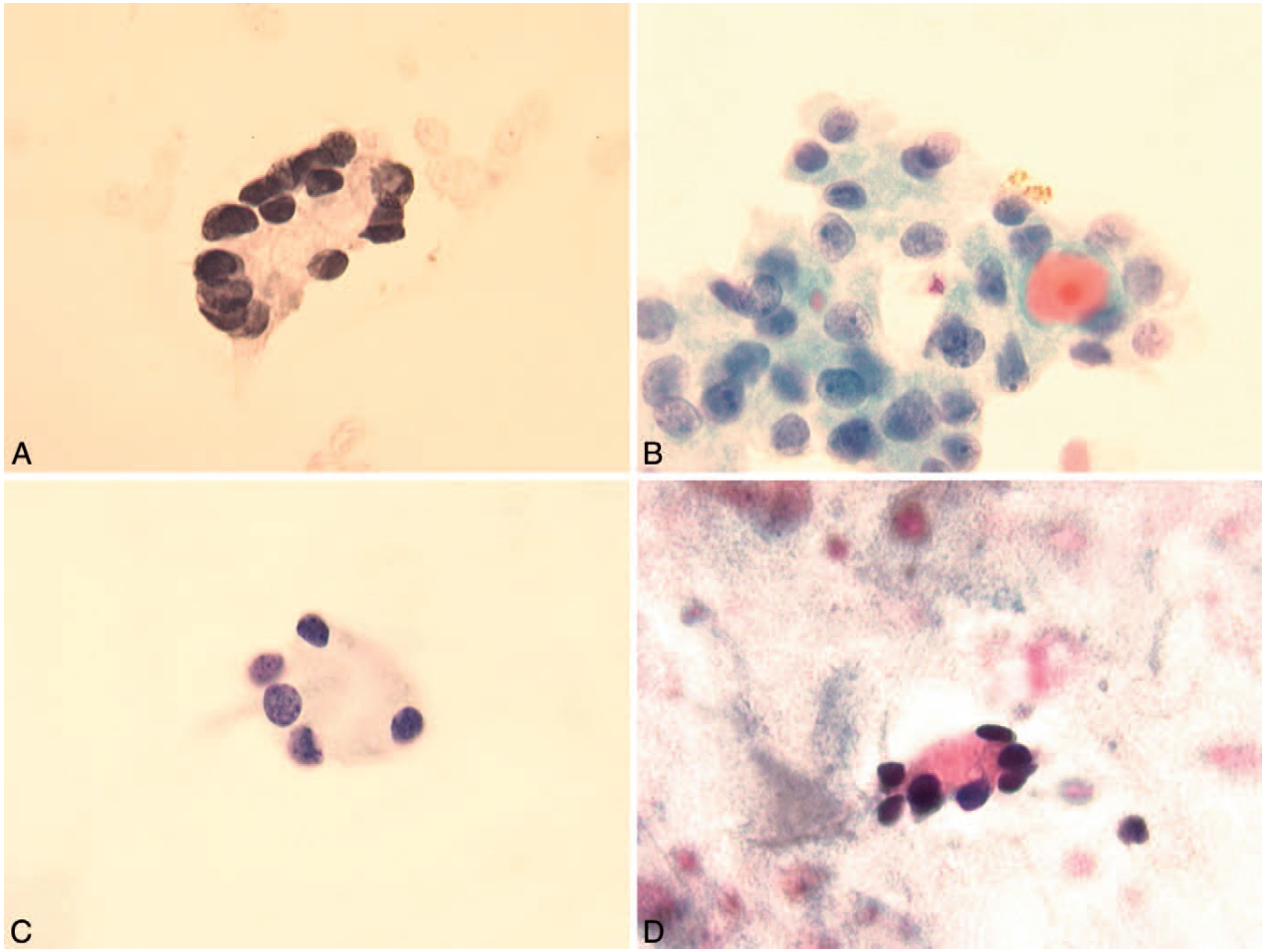
Refining Atypical Diagnoses

- Cytologic atypia more likely to reflect malignancy than microfollicular pattern
- Aspirates should be cellular
- Background for microfollicular lesions should have minimal colloid or macrophages

Defining Microfollciles

- Microfollicles should be flat groups of cells of no more than 15 cells with a central lumen
  (Arch Pathol Lab Med—Vol 130, February 2006)
- Atypia can arise in setting other than neoplasm
  - Following FNA
  - Hyperfunctions (Graves, adenoma)
  - Radiation or chemotherapy (important for patients with nodules identified on staging surveys)
  - Chronic Lymphocytic Thyroiditis

Microfollicles



Interobserver Agreement on Microfollicles in Thyroid Fine-Needle Aspirates Arch Pathol Lab Med—Vol 130, February 2006