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Challenging Cases In Thyroid Cytopathology

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No Disclosures To Report

Learning Objectives

• To understand and apply the Bethesda System diagnostic categories utilized in these cases
• To be familiar with the clinical implications of each of the diagnostic categories
• To know the various molecular abnormalities associated with each lesion discussed
Case #1: 65 y/o Male with Right Thyroid Nodule - Diff Quik

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Case #1: 65 y/o Male with Right Thyroid Nodule - Pap Stain
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Case #1

- Cytopathologic Diagnosis:
  - Atypia of Undetermined Significance
- Reflex Molecular Testing:
  - ThyroSeq v 2: NRAS Mutation Identified
- Follow-up:
  - Right Thyroid Lobectomy
Genetic Alterations Associated with Papillary Thyroid Carcinoma

- 75% of Papillary Thyroid Carcinomas show mutations as follows:
  - 45% - BRAF
  - 15% - RET/PTC
  - 15% - RAS (most often associated with FVPTC and NIFTP)


Genetic Alterations Associated with Follicular Carcinoma

- 70% of Follicular Carcinomas show mutations as follows:
  - 40% - RAS
  - 30% - PAX8/PPARg
  - Rare - BRAF/K601E


Case #1
Right Thyroid Lobectomy
Case #1
Right Thyroid Lobectomy

Case #1
Right Thyroid Lobectomy

Case #1
Right Thyroid Lobectomy
Case #1
Right Thyroid Lobectomy

NON-INVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES (NIFTP)

• Formerly referred to as encapsulated, non-invasive follicular variant of papillary thyroid carcinoma
  • These lesions tend to show indolent biologic behavior
  • These lesions are genetically distinct from Classic PTC
  • Thus, the name of this entity has been changed to better reflect its indolent behavior


NIFTP

Historical Context

• A group of experts were assembled to formally assess the tumor previously known as “noninvasive encapsulated follicular variant of papillary thyroid carcinoma (FVPTC)” to develop diagnostic criteria and study prognosis
  • Based on the group’s consensus findings, the new term “noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)” was announced at the meeting of the Endocrine Pathology Society in March 2015
  • This terminology is included in the new World Health Organization (WHO) classification system for endocrine tumors


NON-INVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES (NIFTP)

- This tumor shows a very high association with other follicular-pattern tumors, with 'RAS mutations the most commonly identified.
- However, PPARγ and BRAF K601E mutations may be seen on occasion.
- BRAF V600E mutations and RET gene fusions that are commonly seen in classical type of papillary carcinoma are not seen in this tumor.

NIFTP Impact on Cytopathology

- The introduction of the NIFTP nomenclature has posed a potential problem for cytopathologists
- Usually, the first specimens obtained from thyroid nodules are FNAs
- Differentiating features of NIFTP from those of PTC can be challenging
- Many worry that making the diagnosis of PTC on FNA can result in a false-positive diagnosis in the case of NIFTP


NIFTP
Impact on Cytopathology

- On FNA specimens with nuclear features of PTC and/or follicular architecture, NIFTP is now in the differential diagnosis
- The evaluation of NIFTP lesions on FNA is difficult
- 29% false-positive rate and 9–58% true predictive value on preoperative assessment of follicular variant tumors


NIFTP – Exclusionary Criteria

- Any capsular or vascular invasion
- True papillary structures comprising greater than 1% of tumor volume
- Psammoma bodies
- Infiltrative border
- Tumor necrosis (not associated with FNA)
- Increased mitoses (defined as at least 3 per 10 HPF)
- Presence of any other papillary thyroid carcinoma variant (e.g., tall cell, columnar cell, cribriform-morular, diffuse sclerosing, etc.) or an oncocytic lesion


Case #2. 46 y/o Female Left Thyroid Nodule Diff Quik
Case #2 – Diff Quik

Case #2 – Diff Quik

Case #2 – Pap Stain
Case #2
Thyroidectomy

Case #2 Left Thyroid
Lymph Node

Case #2
Left Thyroid - Synaptophysin
Case #2 Left Iliac Bone FNA
Pap Stain

Case #2 Left Iliac Bone FNA
Cell Block

Case #2 Left Iliac Bone FNA
Synaptophysin
Medullary Thyroid Carcinoma

- Neuroendocrine tumor derived from C cells (formerly called parafollicular cells) of ultimobranchial body of neural crest, which secrete calcitonin
- Represents 5 - 10% of thyroid carcinomas

- Sporadic (nonhereditary)
  - 75 - 80% of cases
  - Age 40 - 60 years
  - Solitary
  - Often associated with paraneoplastic syndromes (diarrhea from vasoactive intestinal peptide (VIP), Cushing's syndrome), dysphagia and hoarseness from tumor bulk

Marini F, et.al. Multiple Endocrine Neoplasia Type 2. Orphanet J Rare Dis 2006;1:45
Medullary Thyroid Carcinoma

- Hereditary (familial)
  - 20 - 25% of cases
  - Seen in younger patients (mean age 35 years)
  - Associated with MEN 2A and 2B syndromes
    - MEN 2A: MTC, pheochromocytoma and parathyroid hyperplasia
    - MEN 2B: MTC, pheochromocytoma, mucosal and alimentary tract neuromas and marfanoid habitus
  - Can occur without the presence of other endocrinopathies (familial non-MEN MTC)

Marini F, et al. Multiple Endocrine Neoplasia Type 2. Orphanet J Rare Dis 2006;1:45.

- Associated with germ line mutations in RET proto-oncogene, familial medullary thyroid carcinoma syndrome, von Hippel-Lindau disease or neurofibromatosis
- Usually bilateral, multicentric with C-cell hyperplasia
- Usually discovered by screening test for serum calcitonin or peripheral blood RET oncogene mutational analysis

Hereditary Medullary Thyroid Carcinoma

Marini F, et al. Multiple Endocrine Neoplasia Type 2. Orphanet J Rare Dis 2006;1:45.

Medullary Thyroid Carcinoma

- 5 year survival: 86% 1
- Poor Prognostic Factors:
  - Older age, cervical nodal metastases, male, sporadic forms, high mitotic activity, small cell type; somatic RET mutation 2
- Favorable Prognostic Factors:
  - Young age, female, familial forms, microcarcinoma

Case #3: 28 y/o Female Right Thyroid FNA
Diff Quik Stain
Case #3
Cell Block

Case #3
TTF-1 Stain

Case #3
Thyroglobulin Stain
Case #3

- Cytopathologic Diagnosis:
  - Atypia of Undetermined Significance
  - Atypical but markedly degenerated cells identified
- Reflex Molecular Testing (ThyroSeq v2):
  - BRAF Mutation Identified
- Follow-up:
  - Thyroidectomy

BRAF V600E

- Most common genetic alteration in PTC (45%)
- Classic papillary carcinoma, tall cell-variant
- Associated with higher tumor stage at presentation, extra-thyroidal extension, lymph node metastasis, higher rate of tumor recurrence and tumor-related mortality
- Highly specific for PTC
- Also associated with Poorly Differentiated Carcinoma and Anaplastic Ca


Case #3: Thyroidectomy
Case #3: Thyroidectomy

Case #3: Thyroidectomy

Case #3: Thyroidectomy - TTF-1 Stain
Case #3:
Thyroidectomy - Thyroglobulin Stain

Infarcted Papillary Thyroid Carcinoma

- A known but rare phenomenon post-FNA
- Post-FNA infarcted thyroid nodules most often occur in Hurthle cell tumors
- Not well described pre-FNA


Infarcted PTC Following FNA

- Mechanisms have been postulated as to how FNA may cause infarction of a thyroid nodule
- The needle may interrupt the microvasculature or may cause traumatic venous thrombosis
- This may be exacerbated by multiple passes with rigorous aspiration, by extraction of large amounts of tissue, and by a large needle size


Case #4: 61 y/o Male with Right Thyroid Nodule – Diff Quik
Case #4

• Cytopathologic Diagnosis:
  • Atypia of Undermined Significance
  • Reflex Molecular Testing (ThyroSeq v2):
    • Strong expression of Parathyroid Hormone (PTH)

Parathyroid Cells in a “Thyroid” FNA

• With increasing use of thyroid FNA, the chances of encountering unsuspected parathyroid lesions are also increasing
  • A parathyroid lesion may present as a thyroid “incidentaloma”
  • Lesions of the thyroid and parathyroid share many cytomorphologic characteristics, making the distinction between the two difficult

Distinguishing Parathyroid from Thyroid on FNA

• IHC Stains (TTF-1, Thyroglobulin, and PTH) can be helpful and can be performed on destained Pap smears or cell block sections with comparable results
  • A conclusive distinction between thyroid and parathyroid cells is not always possible
  • The cytomorphologic distinction between thyroid and parathyroid can be very subtle

Distinguishing Parathyroid from Thyroid on FNA

- A background of colloid-like substance and macrophages is not a useful distinguishing feature
- The most reliable cytomorphologic feature of parathyroid lesions is the diversity of architectural features
  - Naked nuclei, loose clusters, papillae with fibrovascular cores, and a micro-follicular pattern can be seen in combination
- Nuclear features of parathyroid lesions are subtle
  - Uniform nuclei with stippled chromatin, eccentric nuclei can be seen


Distinguishing Parathyroid from Thyroid on FNA

- Overlapping features and cytopathologic mimics/pitfalls:
  - Intranuclear pseudoinclusions
    - A well-known feature of PTC
    - Can also be seen in parathyroid lesions
  - Papillae
    - Can be seen in both PTC and Parathyroid lesions
  - Micro-follicular pattern
    - Can be seen in both PTC and Parathyroid lesions


Distinguishing Parathyroid from Thyroid on FNA

- Clinicoradiologic Correlation
  - Can be helpful, but has limitations
  - A significant number of patients with parathyroid lesions may have serum PTH levels within normal limits
  - Unusual anatomic location of parathyroids can also lead to diagnostic difficulty
  - Parathyroid glands may be intrathyroidal

Philadelphia Skyline At Night
Photograph by Jon Holiday