Challenging Cases

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Case #1
FNA of nodule in left lobe of thyroid in 67 y.o. woman
DDx of elongated cells in thyroid FNAs

- Papillary Thyroid Carcinoma
  - Tall Cell Variant
  - Columnar Variant
- Medullary Thyroid Carcinoma
- Anaplastic Thyroid Carcinoma
- Metastasis
  - Melanoma
  - Colonic Adenocarcinoma
- Cyst-lining cells
- Ciliated glandular cells from
  - Thyroglossal duct cyst
  - Contaminants from needle tract (trachea)

Cytological Dx
Papillary Thyroid Carcinoma
Comment: The cytological features raise the possibility of the Tall Cell Variant

Final Dx
PTC, Tall Cell Variant
Columnar Cell Variant, PTC

- One of the least common variants of PTC, and occurs primarily in males
- Characterized by columnar cells with hyperchromatic, oval, and pseudostratified nuclei and supranuclear or subnuclear cytoplasmic vacuoles
  - reminiscent of colonic adenoma or secretory-type endometrium

Metastatic Colonic Adenocarcinoma

Columnar Cell Variant, PTC

- Clinico-radiological correlation and/or judicious use of a limited immunopanel including thyroglobulin can solve the problem in difficult cases
- Other thyroid markers such as TTF-1 and PAX8 are also expressed in lung and gynecological carcinomas, respectively, while the intestinal marker CDX-2 is expressed in up to 50% of CCV
- The \textit{BRAF}^{V600E} mutation, which is found in one-third of CCV cases may also be found in a subset of these metastatic carcinomas
Cyst-lining cells
### Immunocytochemistry

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Thyroglobulin</th>
<th>TTF1</th>
<th>Calcitonin</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTC</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MTC</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>CEA+</td>
</tr>
<tr>
<td>Anaplastic Thyroid Ca</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>Chromogranin</td>
</tr>
</tbody>
</table>

### Tall Cell Variant, PTC

- The most common aggressive variant of PTC (1-13%)
- Up to 90% of TCV have the $\text{BRAF}^{V600E}$ mutation
- $\text{TERT}$ promoter mutations are also significantly more prevalent in TCV (31%) compared to conventional PTC (<10%)
  - $\text{TERT}$ promoter mutations play an important role in cellular immortality and tumorigenesis by increasing telomerase activity

### Tall Cell Variant, PTC

- Clinico-pathological studies have shown that >10% of tall cell features within a PTC is already associated with an adverse clinical outcome
  - therefore, the identification of tall cell features should be mentioned, whether it is on thyroid FNA prior to surgical treatment or on final pathology reports

### Case #2

**FNA of nodule in right lobe of thyroid in 69 y.o. woman**
Cytological Dx
Follicular Neoplasm, Hürthle (oncocytic) type

Final diagnosis
Follicular adenoma, Hürthle (oncocytic) type
DDx for Hürthle cell lesions

- Hürthle cell metaplasia in non-neoplastic lesions
  - Nodular goiter
  - Lymphocytic thyroiditis
- Hürthle cell neoplasm
- Hürthle cell metaplasia in neoplastic lesion
  - Papillary Thyroid carcinoma
  - Focal oncocytic changes: common
  - Oncocytic variant
  - Warthin-like variant

Follicular neoplasm, Hürthle cell (oncocytic) type - cytological features

- Moderately to markedly cellular specimens
  - Exclusively (or almost exclusively) composed of Hürthle cells
    - Typically with prominent nucleoli
    - Arranged as single cells and/or syncytial or microfollicular pattern and/or trabeculae

FNA biopsy of Hürthle cell lesions of the thyroid gland-- a cytomorphologic study of 139 cases with statistical analysis


- Evaluated 14 cytological features of benign HCL and HCN
- Cytological features statistically significant

<table>
<thead>
<tr>
<th>UNIVARIATE ANALYSIS</th>
<th>SLR ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-macrofollicular</td>
<td>Non-macrofollicular</td>
</tr>
<tr>
<td>Absence of colloid</td>
<td>Absence of colloid</td>
</tr>
<tr>
<td>No inflammation</td>
<td>No inflammation</td>
</tr>
<tr>
<td>Transgressing BV</td>
<td>Transgressing blood vessels</td>
</tr>
<tr>
<td>&gt;90% Hürthle cells</td>
<td></td>
</tr>
<tr>
<td>&gt;10% single cells</td>
<td></td>
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</tbody>
</table>
Colloid nodule/nodular hyperplasia

Hurthle cell lesion/neoplasm

Lymphocytes

Microfollicles/dyscohesion

Hashimoto thyroiditis/chronic lymphocytic thyroiditis

Colloid, variably sized follicles/sheets


Hurthle cell metaplasia in non-neoplastic lesions

Papillary Thyroid Carcinoma, oncocytic variant versus Hürthle cell neoplasm
FNAC DDx oncocytic neoplasms

<table>
<thead>
<tr>
<th>FNA Features</th>
<th>Oncocytic Variant PTC</th>
<th>Hurthle Cell Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear Inclusions</td>
<td>50%</td>
<td>12%</td>
</tr>
<tr>
<td>Nuclear Grooves</td>
<td>80%</td>
<td>12%</td>
</tr>
<tr>
<td>Prominent Nucleoli</td>
<td>Absent</td>
<td>57%</td>
</tr>
</tbody>
</table>

**FNHCT Management and 2015 ATA guidelines**

- Diagnostic surgical excision (lobectomy) is the long-established standard of care for FNHCT
- After consideration of clinical and US features, molecular testing may be used to supplement malignancy risk assessment data instead of proceeding directly to surgery
  - However, the accuracy of molecular testing may be lower for FNAs of oncocytic lesions
  - There is an increased rate of “suspicious” results in benign oncocytic lesions using the Afirma GEC
    - up to 1/3 of FNHCT have a negative GEC analysis and can be spared surgery
- Mutational analysis in general unhelpful to distinguish Hurthle adenoma from CA
- RET/PTC rearrangements and RAS mutations are seen in both
- PAX8/PPARY are rare in Hürthle cell CA