IT ‘S A MATTER OF...
CASE HISTORY

29 y/o woman

3.2 cm right thyroid nodule in 2018

Previous FNAC diagnosed as “possible mesenchymal neoplasm positive for vimentin” in 2012

FNAC processed by LBC and Conventional cytology
Cytological Findings

Scant colloid

Cellular smears

SEVERAL isolated and few small loosely groups of follicular cells with spindle-elongated features and mild/focal nuclear irregularities

Eosinophilic granular cytoplasm and scant/absent cytoplasm in several cells

Round-oval nuclear shape with spindle-elongated features

Chromatin clearing and perinuclear clearing

Few nuclear grooves

Few nuclear inclusions

Focally, hyaline-globular stromal component
What could I morphologically conclude?

A diagnostic dilemma
POSSIBLE DIFFERENTIAL DIAGNOSIS IN PRESENCE OF SPINDLE-ELONGATED FEATURES..and not only!

<table>
<thead>
<tr>
<th>BENIGN</th>
<th>MALIGNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hashimoto Thyroiditis</td>
<td>1. Papillary Thyroid carcinoma</td>
</tr>
<tr>
<td>2. Riedel Thyroiditis</td>
<td>2. Medullary Thyroid carcinoma</td>
</tr>
<tr>
<td>3. Effect of FNAB</td>
<td>3. Poorly differentiated and/or anaplastic cancer</td>
</tr>
<tr>
<td>4. Follicular neoplasm with spindle areas</td>
<td>4. Metastatic tumor</td>
</tr>
<tr>
<td>5. Clear cell oxyphilic neoplasm</td>
<td></td>
</tr>
<tr>
<td>6. Hyalinizing Trabecular Tumor</td>
<td></td>
</tr>
<tr>
<td>7. Solitary fibrous tumor</td>
<td></td>
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<tr>
<td>8. Smooth muscle tumor</td>
<td></td>
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</tbody>
</table>
PAPILLARY CARCINOMA

- May occur with multiple nodules
- High cellularity
- Follicular clusters or papillary structures
- Medium to large cells with clearing, nuclear pseudoinclusions, grooves
- Possible squamoid metaplasia (focal finding)
- Sometimes bundles of sclerotic tissue
MEDULLARY THYROID CARCINOMA

- Multiple small nodules are frequently observed
- May present with either biphasic or monophasic pattern
- Lack of follicular structures
- Wide range of cellular types (including large, plasmacytoid, spindle-shaped and signet-ring cells)
- Fibrous tissue admixed with cellular clusters
- Amyloid is often present
Criteria

Cellular preparations display an insular, solid, or trabecular cytoarchitecture (Figs. 10.1, 10.2, 10.3, and 10.4).
There is a uniform population of malignant follicular cells with scant cytoplasm (sometimes plasmacytoid) (Fig. 10.5) or with oncocytic features (Fig. 10.6).
The cells have a high nuclear/cytoplasmic (N/C) ratio with variable nuclear atypia (Figs. 10.7 and 10.8).
Colloid is scant.
Apoptosis and mitotic activity are present (Fig. 10.9).
Necrosis is often present (Fig. 10.10).
In liquid-based cytology, PDTC exhibits the same cytomorphology, characterized by a population of cells with a high N/C ratio and focal nuclear atypia (Figs. 10.2 and 10.5).
ANAPLASTIC THYROID CARCINOMA

- Rapidly growing nodule in an elderly patient
- Variable cellularity as isolated and variably sized groups
- Striking cellular and nuclear pleomorphisms with prominent nucleoli
- Necrotic debris and hemorrhagic background with neutrophils (abscess-like)

Mitotic figures
Metastatic lesion

- Cellular smears with cell clusters or sheets
- Medium sized cellularity with variable amount of cytoplasm and/or mucin
- Round to oval nuclei, eccentrically located
- Finely granular and coarse chromatin

Nucleoli may be prominent

ANCILLARY TECHNIQUES
Your diagnosis?

- A) SM
- B) POSITIVE FOR MALIGNANCY-PTC
- C) MTC
- D) FOLLICULAR NEOPLASM WITH SPINDLE FEATURES AND FEW PLEOMORPHIC FINDINGS
Cell block slides-obtained from LBC stored material- were used for ICC:

**Positivity**
- Thyroglobulin
- TTF-1

**Negativity**
- HBME-1
- Galectin-3
- Calcitonin
- CEA
- CD34
- Vimentin
What i had in my hands

- Morphology of follicular proliferation with spindle-elongated features and focal-mild nuclear irregularities

- ICC favoring a thyroid origin

- **BRAFV600E** *wt*
HOW SHOULD I CALL IT?

Follicular neoplasm (HBME-1 and Gal-3 negative)

OR

Papillary Thyroid carcinoma (morphology and IIC not in favor)

OR

Suspicious for malignancy (for the irregularities and don’t care about HBME-1 and Gal-3)
Well differentiated thyroid proliferation with some spindle-elongated features and few mild nuclear pleomorphisms (follicular adenoma? HTT?mesenchimal lesion?)
Histology revealed a 3 cm capsulated nodule

Histological features:

1) Trabecular structures
2) polygonal-spindle cells with irregularities and some grooves but few nuclear pseudo-inclusions
3) cylindrical–ovoid nuclei
4) eosinophilic granular cytoplasm

The IIC resulted in:

**POSITIVITY**
- Thyroglobulin
- TTF-1
- S100
- MIB-1

**NEGATIVITY**
- HBME-1
- Galectin-3
- Calcitonin/mCEA
- β-Catenin
- CK-19
Hyalinizing Trabecular Tumor
• First described in 1895 by Zipkin but introduced as a rare follicular-derived neoplasm in 1987 by Carney

Neoplastic capsulated lesion characterized by trabecular/alveolar pattern with intra-extracellular hyaline material

• Polygonal or elongated/spindle cells
• Nuclear features are very similar to those of PTC

• 20-40% of HTTs show RET/PTC1 rearrangement

• Difficult cytological recognition due to:
  1) Its rarity
  2) Morphological overlapping with PTC
  3) Medullary carcinoma

Sharing features with PTC
## TABLE 2. Comparative Distribution of Hyalinizing Trabecular Tumor Cases According to Cytological Categories per Italian and Bethesda Reporting Systems

<table>
<thead>
<tr>
<th>SIAPEC-IAP classification</th>
<th>TIR 2</th>
<th>TIR 3A</th>
<th>TIR 3B</th>
<th>TIR 4</th>
<th>TIR 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBSRTC</td>
<td>II (benign)</td>
<td>III (AUS/FLUS)</td>
<td>IV (FN/SFN)</td>
<td>V (SFM)</td>
<td>VI (malignant)</td>
</tr>
<tr>
<td>No. of cases (%)</td>
<td>1 (5.5)</td>
<td>4 (22.2)</td>
<td>6 (33.3)</td>
<td>5 (28)</td>
<td>2 (11)</td>
</tr>
</tbody>
</table>

## TABLE 3. Cytomorphological Features of Hyalinizing Trabecular Tumor

<table>
<thead>
<tr>
<th>Feature</th>
<th>Benign</th>
<th>AUS/FLUS</th>
<th>FN/SFN</th>
<th>SFM</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaline material</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Nuclear pseudoinclusions</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Focal</td>
</tr>
<tr>
<td>Nuclear grooves</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Few cells</td>
<td>Few cells</td>
</tr>
<tr>
<td>Mild nuclear atypia</td>
<td>Absent</td>
<td>Focal</td>
<td>Absent/focal</td>
<td>Focal</td>
<td>Some cells</td>
</tr>
<tr>
<td>Severe nuclear atypia</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Focal</td>
<td>Some cells</td>
</tr>
<tr>
<td>Colloid</td>
<td>Focally present</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm; SFM, suspicious for malignancy.
### Table 4. Immunocytochemistry Results for Hyalinizing Trabecular Tumor Cases

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>AUS/FLUS</th>
<th>FN/SFN</th>
<th>SFM</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_+ / G_+$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$H_- / G_-$</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>$H_+ / G_-$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$H_- / G_+$</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm; G, galectin-3; H, HBME-1; SFM, suspicious for malignancy; $+$, positive; $-$, negative.

Values represent the numbers of positive cases. All cases had weak to slightly moderate positivity.

<table>
<thead>
<tr>
<th></th>
<th>MIB-1*</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$+$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>cytokeratin-19</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>$-/+$</td>
<td>$+$</td>
<td>$+$</td>
<td></td>
<td>+/-</td>
</tr>
</tbody>
</table>
GLIS Rearrangement is a Genomic Hallmark of Hyalinizing Trabecular Tumor of the Thyroid Gland

Table 1. Characteristics of Tumors Initially Diagnosed as HTT

<table>
<thead>
<tr>
<th>Fusion type</th>
<th>HTT, current study (n=14)</th>
<th>TCGA study (n=484)</th>
<th>Current study, unselected PTC (n=111)</th>
<th>Current study, aggressive PTC (n=109)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX8–GLIS3</td>
<td>13/14 (93%)</td>
<td>0/484</td>
<td>0/111</td>
<td>0/109</td>
<td>0/704 (0.0%)</td>
</tr>
<tr>
<td>PAX8–GLIS1</td>
<td>1/14 (7%)</td>
<td>0/484</td>
<td>1b/111</td>
<td>0/109</td>
<td>1/704 (0.1%)</td>
</tr>
</tbody>
</table>

a As reported by TCGA Research Network (56).
b The same case was reported as PAX8/GLISI positive in TCGA PanCancer Atlas study (see www.cbioportal.org/).

* Initially diagnosed as HTT, reclassified after blind pathology review.
PTC and MTC are the main morphological pitfalls for HTT on FNAC.

The ICC and BRAF analysis can not achieve a 100% diagnostic accuracy but they might be performed on FNA supporting a more accurate preoperative diagnosis.

Combine morphology and ancillary techniques with clinical and radiological findings.

The detection of GLIS rearrangements, particularly PAX8-GLIS3 is highly prevalent in HTT but not in PTC.

Due to unique genetic mechanisms and an indolent behavior, it is proposed to rename this tumor as “GLIS-rearranged hyalinizing trabecular adenoma.”
THANK YOU

FOR YOUR ATTENTION