Thyroid Follicular Epithelial Cell Lesions

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Thyroid Follicular Epithelial Cell Neoplasms Classification

- Follicular adenoma
- Follicular carcinoma
- Papillary carcinoma
- Poorly-differentiated carcinoma
- Undifferentiated (anaplastic) carcinoma
- Others (rare epithelial carcinomas)
Thyroid Follicular Epithelial Cell Neoplasms

Outline

• Clinical and pathologic features of thyroid follicular epithelial cell lesions:
  – Follicular adenoma:
    • Variants
  – Follicular carcinoma:
    • Invasion: capsular and vascular
    • Variants
Thyroid Gland Epithelial
Cell Neoplasms
Outline Continued

– Atypical Follicular Adenoma
– Poorly-Differentiated Carcinoma
Follicular Adenoma

Definition

- Benign encapsulated tumor with evidence of follicular epithelial cell differentiation showing growth pattern and cytomorphology different from the surrounding thyroid parenchyma, but lacking features of thyroid papillary carcinoma
Follicular Adenoma
Clinical Features

• F > M; occurs over a wide age range most common in the 5th-6th decades of life
• Presentation: painless neck (thyroid) mass; duration of symptoms months to years
• Most often solitary and limited to one part of the thyroid lobe but may involve the entire lobe; rarely, multiple adenomas may be present in a single gland
Follicular Adenoma
Clinical Features

- Patients are usually euthyroid:
  - serum thyroglobulin may be raised but clinical evidence of hyperthyroidism is rarely seen
- Thyroid imaging (I-123 or Technetium-99m)
  - poorly functional or "cold" nodule; adenomas are most often "cold" or hypofunctional nodules
- No specific etiologic factors associated with the development of an adenoma
<table>
<thead>
<tr>
<th>Molecular Alteration</th>
<th>Follicular adenoma or carcinoma (%)</th>
<th>Conventional papillary carcinoma (%)</th>
<th>Follicular variant of papillary carcinoma (%)</th>
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</thead>
<tbody>
<tr>
<td>RET/PTC translocation</td>
<td>0</td>
<td>26–28</td>
<td>3</td>
</tr>
<tr>
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Follicular Adenoma
Differential Diagnosis

- Adenomatoid nodules
- Thyroid papillary carcinoma
- Follicular carcinoma
- Medullary carcinoma
Follicular Adenoma
Differential Diagnosis

- Adenomatoid nodules
- Thyroid papillary carcinoma
- Follicular carcinoma
- Medullary carcinoma
Follicular Adenoma

Histologic Types

- Oncocytic (Hürthle) cell
- Signet ring cell
- Clear cell
- Follicular adenoma with:
  - spindle cells
  - mucinous stroma
  - mesenchymal components
- Hyalinizing trabecular (paraganglioma-like) adenoma
- Atypical follicular adenoma
Hyalinizing Trabecular Adenoma
Definition

- Benign encapsulated tumor with evidence of follicular epithelial cell differentiation showing trabecular and organoid growth patterns, extracellular hyalinization and elongated cells arranged around blood vessels
- “Paraganglioma-like” adenoma; hyalinizing trabecular tumor
Hyalinizing Trabecular Adenoma
Clinical Features

• The demographics and clinical presentation are similar to those of a typical follicular adenoma
Hyalinizing Trabecular Adenoma
Immunohistochemistry

- Cytokeratins, thyroglobulin, TTF-1
- Ki67 cell membrane pattern
- Negative for calcitonin, neuroendocrine markers
Follicular Adenoma
Treatment and Prognosis

• Conservative surgery (lobectomy) is the treatment of choice
• No recurrences or metastases
Hyalinizing Trabecular Adenoma
Variant of Papillary Carcinoma or Not?

• Variant of papillary carcinoma:
  – Nuclear features
  – IHC profile including CK19
  – RET/PTC translocation
  – Nodal metastasis

• Variant of follicular adenoma:
  – Questionable classification
  – CK19 and galectin 3 negative
  – Absence of RET/PTC translocation and BRAF mutation

• Hyalinizing Trabecular Tumor
Follicular Carcinoma
Definition

- Follicular epithelial cell differentiated thyroid neoplasm, not belonging to thyroid papillary carcinoma, with evidence invasion (i.e., capsular and/or vascular invasion) and/or metastatic disease
Follicular Carcinoma
Clinical Features

• 10-20% of all malignant thyroid tumors
• F > M; occurs over a wide age range, including children and adolescents; most common in the 5th-6th decades of life (approximately one decade older than patients with thyroid papillary carcinoma)
• Clinical presentation: solitary, painless neck mass; pain may occur later in the disease course; the initial presentation may be as a pulmonary metastasis or pathologic fracture secondary to osseous metastasis
Follicular Carcinoma

Clinical Features

- Patients are usually euthyroid; uncommonly, patients present with signs and symptoms of hyperthyroidism.
- Incidence is greater in iodine-deficient regions of the world and partly for this reason occurs in glands which have been enlarged for long periods; addition of supplemental iodine to the diet associated with a decrease in the incidence of follicular carcinoma.
- On thyroid scan (123I): solitary, "cold" or hypofunctioning nodules.
Follicular Carcinoma
Clinical Features

• Development of follicular carcinoma has been linked to irradiation and Cowden’s disease

• RAS oncogene mutation; PAX8/PPARγ fusion
## Frequency of various molecular alterations in papillary carcinoma and follicular neoplasms

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Follicular Carcinoma
Invasion

• A diagnosis of follicular carcinoma is predicated on the presence of invasive growth (capsular and/or angioinvasion), extension into adjacent thyroid parenchyma and/or on the presence of metastatic tumor

• Histologic definition of invasion includes capsular invasion and angioinvasion
Follicular Carcinoma
Capsular Invasion

• Extent of capsular invasion is a source of contention:
  – any degree of invasion into the capsule qualifies categorization as minimally invasive follicular carcinoma;
  – tumor has to penetrate the entire thickness of the capsule to be regarded as unequivocal evidence of capsular invasion.

• Elastic stains may be helpful
Follicular Carcinoma
Capsular Invasion

- Problematic features relative to diagnostic interpretation include:
  - irregular contour(s) of the tumor;
  - tangential sectioning;
  - separate nodule lying immediately outside the capsule of the main tumor mass:
    - in this setting, serial sections to determine whether there is a connection present or not are indicated;
    - presence of continuity between the main mass and the nodule outside the capsule would be indicative of a carcinoma;
    - absence of any connection does not exclude a diagnosis of carcinoma
    - may be indicative of multiple adenomatoid nodules
Follicular Carcinoma
Angioinvasion

• More reliable feature of malignancy than capsular invasion
• Tumor within an involved blood vessel located within or beyond the fibrous capsule
• Presence of tumor within an endothelial-lined space:
  – presence of tumor adherent to the wall with associated thrombus formation
  – tumor cells protruding into a vascular space with an endothelial layer identified over the bulging tumor nests should be regarded as invasive
• Presence of tumor within the fibrous capsule conforming to the contour of a blood vessel (rounded edges) suggests angioinvasion; deeper sections and/or elastic stains may demonstrate the presence endothelial lining or elastic membranes
Follicular Carcinoma
Angioinvasion

- Represents a more reliable feature of malignancy than capsular invasion; since nodal metastasis is rare in association with follicular carcinoma, the invaded vascular space are not lymphatics.

- Some authorities have advocated dividing follicular carcinomas with angioinvasion (with or without capsular invasion) as *moderately invasive* follicular carcinomas as opposed to *minimally invasive* follicular carcinoma that have capsular invasion without angioinvasion and *widely invasive* follicular carcinomas with extensive invasion.
Follicular Carcinoma Categorization

- Based on the extent of the invasive component, two types of follicular carcinoma are recognized differing in their biologic behavior and in their treatment:
  - minimally invasive (low-grade) follicular carcinoma, which in turn can be subdivided into:
    - with capsular invasion only;
    - with angioinvasion:
      - limited angioinvasion, including less than 4 vascular spaces;
      - extensive angioinvasion, including 4 or more vascular spaces.
    - widely invasive follicular carcinoma
Follicular Carcinoma
Differential Diagnosis

• Follicular adenoma
• Dominant adenomatoid nodule
• Thyroid papillary carcinoma
• Thyroid medullary carcinoma
Follicular Adenoma v Follicular Carcinoma
Tissue Sectioning

- Ideally submit the entire lesion to include all of the tumor-to-capsule-to-parenchyma interface
- Not practical for larger tumors:
  - minimum of 10 blocks
  - International Workshop on Thyroid Pathology:
    - Encapsulated follicular neoplasm - at least 5 blocks;
    - Low cellularity, large follicles, edematous stroma and no invasion = FA
    - Encapsulated, increased cellularity and/or other suspicious features – at least 5 additional blocks
Follicular Carcinoma
Histologic Types

- Oncocytic (Hürthle) cell
- Signet ring cell
- Clear cell
- Mucinous variant
- Hyalinizing trabecular carcinoma
Follicular Carcinoma
Histologic Types

- **Oncocytic (Hürthle) cell:**
  - higher prevalence of aggressive behavior and biologic features
  - older age group size and larger size (≥4cm strongly correlated to malignancy)
  - greater inclination to regional node and distant metastases;
  - rarely uptake RAI avidly
  - different genetic alterations by molecular studies (higher frequency of ras mutations)
Follicular Carcinoma, Oncocytic (Hürthle) Cell Type

- Frequency of malignancy is higher (35%) as compared with non-Hürthle cell follicular neoplasms:
  - older age group
  - larger size (≥4cm strongly correlated to malignancy)
  - higher frequency of extrathyroidal extension, local recurrence and distant metastasis
  - lower survival rate
Follicular Carcinoma, Oncocytic (Hürthle) Cell Type

- When stratified according to extent of invasion, no differences in behavior between oncocytic type versus non-oncocytic types of follicular carcinoma.
Another contentious issue is the appropriate mode of therapy. Treatment options include conservative treatment versus more radical approaches:

- **Conservative therapy** - limited resection (lobectomy or subtotal thyroidectomy) without radioactive iodine;
- **Radical therapeutic intervention** - total thyroidectomy followed by administration of radioactive iodine;
- The only caveat to utilizing conservative modalities is the presence of limited invasion and the absence of metastatic tumor:
  - in the presence of metastasis, treatment includes radioactive iodine.
Follicular Carcinoma, Minimally Invasive Treatment and Prognosis

- Prognosis is excellent with 70-100% 10-year survival rates (cure rates reported to be >95%); however, the prognosis may be dependent on whether the tumor demonstrates only capsular invasion or whether there is angioinvasion:
  - for those tumors showing only capsular invasion the long term prognosis is excellent with very low likelihood of metastatic disease (approximately 0.1%);
  - for those tumors with angioinvasion the prognosis is guarded since there is an increase incidence of metastatic disease, albeit approximately 5%:
    - prognosis for limited angioinvasion is considered excellent;
    - prognosis for extensive angioinvasion is guarded
- In the presence of metastatic disease the 10 year survival rate is approximately 50%
Follicular Carcinoma, Widely Invasive Treatment and Prognosis

• Aggressive management is indicated and includes total thyroidectomy and radioactive iodine therapy
• Prognosis varies but is generally considered to be poor:
  – These tumors tend to disseminate hematogenously with metastasis to osseous sites, lungs and brain; cutaneous metastasis also occur;
  – Metastatic disease may be identified at the initial presentation;
• Metastatic tumor is treated with radioactive iodine therapy which may offer long-term palliation but not a cure
• The metastatic foci are histologically similar to the primary tumor and may appear bland lacking cytologic atypia
Follicular Carcinoma, Widely Invasive Treatment and Prognosis

- Survival statistics rival those of poorly-differentiated thyroid carcinomas with 25-45% 10-year survival rates
- Adverse prognostic factors include:
  - presence of extraglandular spread into adjacent soft tissues;
  - presence of distant metastasis;
  - older age of the patient (over 40 years);
  - male gender may be associated with a worse prognosis;
  - extensive intrathyroidal invasion;
  - presence of intravascular invasion;
  - tumor size: tumors greater than 3.5 to 6 cm have a worse prognosis
## Categories of Follicular Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Minimally Invasive</th>
<th>Widely Invasive (Frankly Invasive)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Capsular Invasion Only</td>
<td>With Limited (&lt;4) Vascular Invasion</td>
</tr>
<tr>
<td>Diagnostic criteria</td>
<td>Encapsulated tumor with Capsular invasion only; no vascular invasion</td>
<td>Invasion of &lt;4 blood vessels, with or without capsular invasion</td>
</tr>
<tr>
<td>Mean age at diagnosis</td>
<td>Younger (47-50 yr)</td>
<td>Younger (47-50 yr)</td>
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<tr>
<td>Local recurrence</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Regional lymph node metastasis</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>~0%</td>
<td>Rare (5%), and often delayed</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>~0%</td>
<td>3%-5%</td>
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<td></td>
<td></td>
<td>18%</td>
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Atypical Follicular Adenoma
Definition

- Any encapsulated follicular neoplasm that lacks features for thyroid papillary carcinoma but shows histologic features suspicious for a more aggressive neoplasm (carcinoma) without definitive evidence of either capsular or vascular space invasion
- Synonyms: Atypical follicular neoplasm; follicular tumor of uncertain malignant potential; well-differentiated (follicular) tumor of uncertain malignant potential
Atypical Follicular Adenoma
Clinical Features

• The demographics and clinical presentation of an atypical follicular adenoma are similar to those of a (typical) follicular adenoma
Atypical Follicular Adenoma
Pathology

• Macroscopic and FNAB features of an atypical follicular adenoma are similar to those of a (typical) follicular adenoma.

• Histologic features that should raise the possibility of a potentially more aggressive follicular neoplasm (i.e., carcinoma) include:
  – thickened capsule
  – irregular growth along the peripheral (tumor-to-capsule interface) aspects of the tumor
  – increased mitotic activity (especially with atypical forms)
  – nuclear atypia with prominent nucleoli, giant cells or unusual histologic patterns (spindle cell fascicles)
  – necrosis (in the absence of a previous FNAB)
Follicular Neoplasm of Uncertain Malignant Potential

- The interpretation of what constitutes capsular invasion is still controversial with a lack of consensus among experts as to the diagnostic criteria for capsular invasion.
- The designation of follicular neoplasm of uncertain malignant potential introduced for those tumors in which there is limited capsular invasion (absence of complete capsular transgression), absence of angioinvasion, absence of nuclear features of papillary carcinoma.
Atypical Follicular Adenoma

- According to some authorities, categorization of a tumor as being atypical or of uncertain malignant potential may include encapsulated follicular tumors in which tumor extends only to the inner half of its capsule without angioinvasion and without nuclear features of papillary carcinoma.

- Encapsulated follicular neoplasm showing nuclear features suggestive of but insufficient for diagnosis of follicular variant of papillary carcinoma.
Atypical Follicular Adenoma
Treatment and Prognosis

- Treatment is surgical removal (similar to usual types of follicular adenomas)
- Generally, the surgery is conservative in extent limited to the affected portion(s) of the thyroid gland (lobectomy or subtotal thyroidectomy)
- Long term prognosis is excellent; long term follow-up shows the atypical follicular adenoma to have a benign course but close clinical follow-up is advised (e.g. physical exam, imaging, serum thyroglobulin)
Poorly-Differentiated Thyroid Carcinoma
Definition

- Thyroid neoplasm with histologic and biologic features intermediate between those of differentiated thyroid carcinomas and undifferentiated (anaplastic) carcinoma
Poorly-Differentiated Thyroid Carcinoma
Clinical Features

• Predominantly middle-aged and elderly adults (mean 54 years)
• F>M
• Enlarging neck mass:
  – de novo
  – preceding history of long-standing thyroid mass with transformation from differentiated carcinoma
• Often present with locally advanced disease
Poorly-Differentiated Thyroid Carcinoma
Pathology

• Often large (>4cm), encapsulated or invasive
• Histopathology:
  – insular, solid, diffuse sheets, trabeculae, festoons, follicular, papillary
• Cytomorphology:
  – Uniform, small and monotonous to enlarged and pleomorphic tumor cells
  – Coarse nuclear chromatin
  – Increased mitotic activity and necrosis
  – Colloid-filled follicles can be seen
Poorly-Differentiated Thyroid Carcinoma
Pathology Continued

• Invasive growth including:
  – capsular invasion
  – lymph-vascular invasion
  – extrathyroidal extension
Poorly-Differentiated Thyroid Carcinoma
Immunohistochemistry

- Cytokeratins, thyroglobulin and TTF1
- Calcitonin negative
- Absence of neuroendocrine markers
- Bcl-2 positive
- Increased proliferation rate (Ki67 or MIB1)
Thyroid Lesions with “Insular” Growth

• Not restricted to Follicular Carcinoma:
  – Thyroid Papillary Carcinoma
  – Follicular Adenoma
  – Non-neoplastic Lesions

• Not an indicator of:
  – more aggressive neoplasm
  – a neoplastic proliferation

Jorda et al: Arch Pathol Lab Med 1993117:631-635
Poorly-Differentiated Thyroid Carcinoma
Turin Proposal*

- Presence of solid, trabecular or insular growth
- Absence of nuclear features diagnostic for papillary carcinoma
- Presence of at least one of the following:
  - Convoluted nuclei;
  - Mitotic activity $\geq 3$ mitoses per 10 HPF;
  - Tumor necrosis

* Volante et al. AJSP 2007;31:1256-1264
Poorly-Differentiated Thyroid Carcinoma
Treatment and Prognosis

• Total thyroidectomy and radioactive iodine
• Extrathyroidal extension at presentation in >50%
• Nodal and distant metastasis at presentation in 40% and 30%, respectively
• Recurrence and metastasis occur after treatment in a high percentage of cases
• 5-year survival approximately 50%
• Poor prognosis: advanced age, large tumor size, extrathyroidal extension, metastasis
Poorly-Differentiated Thyroid Carcinoma
Differential Diagnosis

- Medullary carcinoma
- Papillary carcinoma, solid variant
- Undifferentiated (anaplastic) carcinoma
Poorly-Differentiated Thyroid Carcinoma
Differential Diagnosis

• Undifferentiated (anaplastic) carcinoma:
  – Rapidly enlarging neck mass
  – Long-standing history of thyroid-based mass
  – Absence of follicular differentiation by light microscopy and IHC
  – Rapid death due to locally uncontrollable disease:
    • median survival 3 - 4 months
    • 5-year survival 3.6 - 10%
Thyroid Follicular Epithelial Cell Neoplasms

Conclusions

- Discuss and identify criteria for diagnosis of
  - Follicular adenoma and variants
  - Follicular carcinoma and variants
  - Poorly-differentiated thyroid carcinoma