Anaplastic Thyroid Carcinoma (ATC)

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Basis of this lecture

- Dissecting Anaplastic Thyroid Carcinoma: A Comprehensive Clinical, Histologic, Immunophenotypic, and Molecular Study of 360 Cases

Outline

• The basics:
  – Clinical presentation
  – Pathologic features
  – Immunohistochemistry
  – Differential diagnosis

• Recent advances:
  – Prognostic and predictive biomarkers
  – Molecular profile
  – Targeted therapy
Anaplastic thyroid carcinoma (ATC)

- WHO definition: a highly aggressive thyroid malignancy composed of undifferentiated follicular thyroid cells.

- The Roles of pathologists:
  - Traditional: making the right diagnosis
  - New roles: providing prognostic and/or predictive information, including actionable molecular targets.
The basics of ATC: clinical presentation

- **Large rapidly-enlarging thyroid-based (necrotic) mass**
- **Affects patients in their 60-70s (median 68, range 29-99)**
- **Infrequent (<2%) in patients under 40 (including a few case reports in pediatric patients)**
  - Other diagnostic possibility should be considered.
  - ATC diagnosis is pediatric patients is highly debatable
- **Nearly always fatal**: median survival: 3 months; 1-year survival 20%
  - Multimodality treatment in referral centers: median survival ~9 months; 1-year survival ~35%

The majority of ATC are associated with a differentiated thyroid carcinoma

- ~60% of ATC have either a history of previously resected or co-existing differentiated thyroid carcinoma (DTC) component:
  - Well-differentiated
    - Papillary thyroid carcinoma (PTC) most common (75%), in particular tall cell variant
    - Hurthle cell carcinoma (10%)
    - Follicular carcinoma (5%)
  - Poorly differentiated thyroid carcinoma (35%)

ATC with adjacent PTC
ATC with adjacent Hurthle cell carcinoma (HCC)
The basics of ATC: typical histologic features

- Marked pleomorphism
- High mitotic index (>5/10 HPFs in 70%)
- Atypical mitosis (85%)

- Caveat: mitotic rate can be low
  - A mitotic index of ≤5/10 HPFs can be seen in 30% of ATC and 22% of resected ATC
  - In such cases, a diagnosis of ATC can be rendered based on:
    - Other histologic features: e.g. marked nuclear pleomorphism
    - Loss of immunohistochemical evidence of thyroid follicular differentiation
The basics of ATC: typical histologic features

- Tumor necrosis (86%)
- Abundant inflammatory infiltrates (esp. neutrophils and macrophages, 71%)
The basics of ATC: typical histologic features

- Widely invasive, often with gross extrathyroidal extension (90%)
- Lymphovasular invasion (79%)
  - Including invasion of vessel wall
ATC: cytologic features

Spindle 26% (& cellular)

Spindle (& paucicellular)

Spindle (with myxoid stroma)
Pleomorphic (23%)

Squamous (21%)

Epithelial/epithelioid (19%)
Rhabdoid (8%)

Osteoclast giant cell rich (3%)

Heterologous component (<1%)

Osteosarcomatoid

Chondrosarcomatoid
Mixture of morphologic features within one ATC

Osteoclast giant cell rich area

Squamous area
Cytoarchitectural features of ATC do not impact outcome

- Dominant cytologic features did not impact survival
- Paucicellular variant of ATC may have an improved survival: scanty evidence to draw any convincing conclusion.

Xu et al. 2020 Thyroid 30:1505-1517.
Immunoprofile of ATC

Mutation proteins
- BRAF V600E 40%
- (N)RAS Q61R 15%
- Aberrant p53 60%

Differentiation
- 0-4% Thyroglobulin (TG)
- 30% TTF-1
- 54% PAX8 monoclonal
- 70% PAX8 polyclonal
- 75% Any keratin

Mutation proteins
- 68% CAM5.2
- 67% AE1/3
- 65% CK18
- 55% CK5/6
- 47% 34βE12

In practice: a combination of
- Keratins, TTF-1, TG, & PAX8
- BRAF V600E/NRAS Q61R
- ±Ki67, p53

High Ki67: median 50% (range 10-100%)

References:
- Xu et al. 2020 Thyroid 30:1505-1517
- Suzuki et al, Endocrine journal 2015 62: 991-995
- Nonaka et al. Mod Pathol 2008 21: 192-200
- Rivera et al. Acta cytologica 2010 54: 668-672
- Rushton et al. 2016 Histopathology 69: 524-526
- Ghossein et al. 2013 JCEM 98: E1414-1421
NRAS Q61R IHC (− for melanoma marker, CK, TTF-1, TG & PAX8)
Differential diagnosis

**Squamous ATC**
- **Malignant:**
  - Squamous cell carcinoma (extension from larynx)
  - Mucoepidermoid carcinoma
  - Sclerosing mucoepidermoid carcinoma with eosinophilia
- **Benign:**
  - Squamous metaplasia

**Spindle/pleomorphic ATC**
- **Malignant:**
  - Medullary thyroid carcinoma
  - PTC Spindle variant
  - Sarcoma (primary or met.)
  - SETTLE
- **Benign:**
  - Post-FNA spindle cell nodule
  - Endocrine atypia
  - Adenoma with spindle cell metaplasia

**Epithelial/epithelioid ATC**
- **Malignant:**
  - Metastasis
  - NUT carcinoma
  - Adamantinoma-like Ewing
  - Sarcoma
  - Lymphoma
Squamous ATC vs. laryngeal squamous cell carcinoma

Similarity:
• True keratinization & intercellular bridge
• Immunoexpression of squamous markers: p40, p63, HMWCK

Pathologic clues towards ATC:
• High frequency (91%) of PAX8 positivity
• High frequency (87.5%) of BRAF V600E mutation
• Differentiated thyroid carcinoma component/history (95%) in particular tall cell variant of PTC

Xu et al. 2020 Thyroid 30:1505-1517.
Association between pure squamous ATC & PTC TCV

95% of pure squamous ATCs have a history or coexisting PTC
- 69% is tall cell variant

Bronner MP, LiVolsi VA. Mod Pathol 4:637, 1991
Xu et al. 2020 Thyroid 30:1505-1517.
Thyroid squamous cell carcinoma: a subtype of ATC (WHO 2022)

- Defined as a separate entity in WHO 2017:
  - Comprised entirely of tumor cells with squamous differentiation
  - No evidence of other type of thyroid carcinoma

- Similar molecular profile as other ATC
  - $BRAF^V600E$ 60%

- Similar outcome as other ATCs
  - Median overall survival 14 months (vs. 10 months)

Xu et al. 2020 Thyroid 30:1505-1517.
# Squamous ATC vs. squamous metaplasia

<table>
<thead>
<tr>
<th></th>
<th>Squamous metaplasia</th>
<th>Squamous ATC</th>
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<tbody>
<tr>
<td><strong>Similarity</strong></td>
<td>Keratin pearls, intercellular bridge</td>
<td>Both can be BRAF V600E positive</td>
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<tr>
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<td>(+) IHC: CK5/6, 34BE12, p63, p40, <strong>PAX8</strong></td>
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<td>(-) IHC: TTF-1, thyroglobulin</td>
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<tr>
<td><strong>Difference</strong></td>
<td>Focal, adjacent to FNA cavity</td>
<td>Extensive</td>
</tr>
<tr>
<td>• Histology</td>
<td>Absent</td>
<td>Present w/ atypical form</td>
</tr>
<tr>
<td>• Mitosis</td>
<td>Absent</td>
<td>Present – marked</td>
</tr>
<tr>
<td>• Nuclear</td>
<td>No abnormal expression</td>
<td>Abnormal (60%)</td>
</tr>
<tr>
<td>pleomorphism</td>
<td></td>
<td>Elevated</td>
</tr>
<tr>
<td>• P53 IHC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ki67</td>
<td>Focal, adjacent to FNA cavity</td>
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<tr>
<td>compared with</td>
<td>Absent</td>
<td></td>
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<tr>
<td>background</td>
<td>No abnormal expression</td>
<td></td>
</tr>
<tr>
<td>lesion</td>
<td>Not elevated</td>
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Focal squamous area immediate adjacent to FNA cavity. Bland cytology, lack pleomorphism and mitotic activity.
Squamous ATC

- Extensive squamous area
- Nuclear pleomorphism
- Necrosis, mitosis
- Absence of FNA changes

PNI or LVI}

Necrosis
Malignant:
- Medullary thyroid carcinoma
- PTC Spindle cell variant
- Sarcoma (primary or met.)
- Spindle epithelial tumor with thymus-like differentiation

Benign:
- Endocrine atypia/RAI-related atypia
- Post-FNA spindle cell nodule
- Follicular adenoma with spindle cell metaplasia
Endocrine atypia

- Bizarre pleomorphic nuclei with smudgy chromatin
- Can be seen in benign or malignant lesions
- Lacks mitosis/necrosis
- Retains TTF-1 & thyroglobulin
- Lacks abnormal p53 expression
Post-FNA spindle cell nodule

- Spindle cell (myofibroblast) proliferation immediate adjacent to FNA site
- No pleomorphism, mitosis, or necrosis
- IHC shows myofibroblast differentiation and lack BRAF V600E mutation

Baloch ZW, Wu H, LiVolsi VA. AJCP 1999 111: 70-74
PTC spindle cell variant

Spindle cell metaplasia in follicular adenoma

- No pleomorphism, mitosis, or necrosis
- IHC: retain of thyroid follicular differentiation (TG+, TTF1+, PAX8+)
## Angiosarcoma of thyroid

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<th>Angiosarcoma</th>
<th>ATC</th>
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<tbody>
<tr>
<td><strong>Similarity</strong></td>
<td>Common in areas of endemic goiter</td>
<td>Elder patients</td>
</tr>
<tr>
<td></td>
<td>Rapidly fatal</td>
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<td></td>
<td>May be cytokeratin positive</td>
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<td></td>
<td>TTF-1/TG negative</td>
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<td><strong>Difference</strong></td>
<td>Vascular lumen (+) CD31/ERG</td>
<td>(+) BRAF/RAS</td>
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Clinical history/suspicion and IHC work up are crucial for diagnosis.

**Malignant:**
- Metastasis
- Lymphoma
- Adamantinoma-like Ewing Sarcoma
- NUT carcinoma
59F, rapidly enlarging thyroid mass

Diagnosis: DLBCL
63M, diffuse thyroid enlargement & cervical/mediastinal lymphadenopathy

Extensive LVI →
63M, diffuse thyroid enlargement & cervical/mediastinal lymphadenopathy

**Diagnosis:** Metastatic NSCLC

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**Metastasis to thyroid gland**

<1% of thyroid malignancy

Common primary sites:
- Clear cell renal cell carcinoma
- Lung
- Breast
- Lower GI
- Melanoma

May present as solitary thyroid mass, sometimes prior to the diagnosis of primary tumor

16-year-old, thyroid mass
Adamantinoma-like Ewing sarcoma  (Bishop et al. AJSP 2015 39: 1267-74)
Carcinoma of the thyroid with Ewing family tumor elements  (Oliveira et al. Virchows Arch. 2017 270: 517-25)

• Young patients (16-42 years)
• Positive IHC: NKX2.2, CD99, AE1/AE3, squamous markers (e.g. p40)
• Outcome better than traditional Ewing sarcoma

FISH/NGS confirmed *EWSR1-FLI1* rearrangement
It is prognostically prudent to report encapsulation, size and % of ATC in primary resected ATC

Pathologic factors that are associated with improved survival on univariate analysis

• Smaller size and percentage of ATC
• Encapsulation
• Negative pathologic (microscopic) margin

Independent prognostic factors are:

• Age at diagnosis,
• Resectability,
• Chemotherapy
• Gross residual disease in resected primary ATC

Xu et al. 2020 Thyroid 30:1505-1517.
New advances: Molecular profile of ATC

ATC has same driver mutations as differentiated thyroid carcinoma:
- **BRAF**, especially V600E: 38%
- **RAS**: 27%

ATC accumulates additional mutations:
- **TP53**: 63%
- **TERT** promoter mutation: 50%
- PI3K-AKT-mTOR 39%
  - **PIK3CA**: 13%
  - **PTEN**: 11%

**References**
- Ravi et al. 2019 Cancers 11.
- Xu et al. 2020 Thyroid 30:1505-1517.
Double-mutated (BRAF/RAS+TERT) ATC is associated with worse outcome

Xu et al. 2020 Thyroid 30:1505-1517.
Targeted therapies in ATC

• Multikinase inhibitors: sorafenib, pazopanib, imatinib, lenvatinib, sunitinib
• BRAF inhibitors: vemurafenib
• MEK inhibitors: trametinib
• PI3K/mTOR inhibitors: everolimus
• EGFR inhibitors: gefitinib
• VEGF inhibitors: axitinib

Ljubas et al., Cancers (Basel), 2019, review, 11(7).
Neoadjuvant Dabrafenib (BRAF inhibitor) and Trametinib (MEK inhibitor) in \textit{BRAF V600E}-mutated ATC

- Feasibility of complete surgical resection
- High pathologic response rate
- Durable locoregional control
- FDA approved and now a standard treatment for \textit{BRAF V600E}-mutated ATC
Pre-treatment

Treatment effects as extensive fibrosis

ATC response rate: 100% to 10%

Residual differentiated thyroid carcinoma
2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer

American Thyroid Association Anaplastic Thyroid Cancer Guidelines Task Force

Clinical Trials are strongly recommended if available
Best Supportive Care/Hospice option can be elected at any point

IVA
- Encourage definitive-intention therapy (because of potential for long-term survival for IVA patients)

Surgery
- Goal: R0/R1 resection
- Avoid debulking
- Avoid laryngectomy

Definitive intention radiation (IMRT) +/- Chemotherapy (taxane monotherapy or with platin or anthracycline)

Targeted therapy (e.g. fusions, ALK: crizotinib, ceritinib, alectinib; RET: pralsetinib, selpercatinib; NTRK: larotrectinib, entrectinib)

IVB
- Resectable?
  - Y: Rapid BRAF assessment (IHC, molecular), parallel Comprehensive genetic testing
  - N: BRAFV600E mut present?
     - Y: Dabrafenib + Trametinib
     - N: Other tumor genetics? e.g. ALK, NTRK, RET fusions

Surgery (if feasible)
- Y: Excellent tumor response?
  - Y: Palliative Chemotherapy and/or Radiation
  - N or Or:
    - Y:
      - Or: Best Supportive Care/Hospice
    - N:
      - Or: Best Supportive Care/Hospice

Y: generally preferred
N: else
BRAF V600E IHC is a sensitive & specific screening tool for BRAF mutation in ATC

- Sensitivity: 95%
- Specificity: 100%

<table>
<thead>
<tr>
<th>BRAF V600E IHC</th>
<th>BRAF V600E mutation</th>
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<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>Positive</td>
</tr>
<tr>
<td>IHC</td>
<td>Negative</td>
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Xu et al. 2020 Thyroid 30:1505-1517.
Immune checkpoint inhibitors in ATC

- PD-L1 positivity in 22-28% ATC

- High PD-L1 tumor cell (TC) expression in *BRAF*-mutated ATC

- A trend towards worse PFS and OS in ATC with high PD-L1 expression (>33% tumor cells)

- Early results from multiple phase I and II studies on immune checkpoint inhibitors in ATC are disappointing

- Currently, there is no guideline or criteria of PD-L1 in ATC.
  - Perform per clinical requests only
  - Report combined positive score (CPS)
Take home messages

• ATC can have various histologic features, but they are not prognostically significant.

• It is important for pathologist to report encapsulation, margin, percentage and size of ATC in resected primary ATC.
  – However, the only independent prognostic factors in ATC are age, resectability, gross residual disease and chemotherapy.

• BRAF V600E immunostain is useful for:
  – Diagnosis & differential diagnosis.
  – For rapid assessment of BRAF V600E mutation status for dabrafenib and trametinib treatment (a crucial and urgent step in ATC work up).
Thank you!