POORLY DIFFERENTIATED, HIGH GRADE AND ANAPLASTIC CARCINOMAS: WHAT IS EVERYONE TALKING ABOUT?
AGGRESSIVE THYROID CANCERS

- PAPILLARY CARCINOMA CERTAIN SUBTYPES
- POORLY DIFFERENTIATED CARCINOMA
- HIGH GRADE DIFFERENTIATED CARCINOMA
- HURTLE CELL CARCINOMA
- ANAPLASTIC CARCINOMA
- MEDULLARY CARCINOMA
PAPILLARY THYROID CARCINOMA

● SUBTYPES
  ○ TALL CELL
  ○ COLUMNAR
  ○ DIFFUSE SCLEROSIS VARIANT
  ○ SOLID VARIANT
  ○ HOBNAIL CELL VARIANT
  ○ MICROPAPILLARY VARIANT
  ○ PROGNOSIS WORSE THAN USUAL PTC
AGGRESSIVE THYROID CARCINOMA

- AGGRESSIVE FEATURES DESPITE TYPE
  - Necrosis
  - Mitotic activity
  - Abnormal mitoses
  - CYTOLOGIC Pleomorphism (must be distinguished from random nuclear atypia which is equivalent to “ancient change” in Schwannomas ((often seen in Hurthle cell nodules)))
POORLY DIFFERENTIATED THYROID CARCINOMA

- There are two major subtypes
- Tumors can be poorly differentiated by:

  - HISTOLOGIC PATTERN  Turin 2007
  - GRADING  (Akslen 2000; Tallini 2011)
POORLY DIFFERENTIATED THYROID CARCINOMA

- **Histologic Pattern**
  - Solid, trabecular or insular
  - Mitoses easily found
  - Abnormal mitoses
  - Necrosis
  - Often large extrathyroidal tumors
  - Vascular invasion
  - Mortality >50% at 5 years.
POORLY DIFFERENTIATED THYROID CARCINOMA

- **HISTOLOGIC PATTERN** Turin 2007

- Often have well differentiated tumor at edge
  - Papillary
  - Follicular variant
  - Follicular
  - Hurthle cell
VASCULARITY
POORLY DIFFERENTIATED CARCINOMA

- Patterns
  - Solid
  - Trabecular
  - Insular
HIGH GRADE THYROID CARCINOMA

- **GRADING**
- Less well known or studied
- These tumors are recognizable by pattern as papillary, follicular, Hurthle
- Have “bad” features—necrosis, mitoses, much vascular invasion

Tallini *Endo Pathol* 2011
HIGH GRADE THYROID CARCINOMA

WHAT DOES IT MEAN TO GRADE THYROID CARCINOMA?

By definition grading in tumors refers to closeness of resemblance of the tumor to the organ or tissue of origin.

In the thyroid this would refer only to follicular carcinoma which is quite rare. So in order to suggest grading in the common tumor subtype papillary carcinoma, other features are needed.
GRADING THYROID CARCINOMA

- No longterm followup studies with multivariate analysis to determine prognostic importance of GRADING in papillary carcinoma.
- Data so far anecdotal.
POORLY DIFFERENTIATED THYROID CARCINOMA

● MOLECULAR FINDINGS

● ARE AS CONFUSING AS THE DEFINITIONS OF PD THYROID CARCINOMA!!

○ 1. If residual papillary ca or follicular variant, may see ret/PTC translocations or Braf mutations

○ 2. If no PTC then most common molecular change is mutation in N-Ras (about 23%)
HIGH GRADE AND POORLY DIFFERENTIATED THYROID CARCINOMA

HIGH GRADE - RETAIN PAPILLARY PATTERN but ADD NUCLEAR PLEOMORPHISM, MITOTIC ACTIVITY AND NECROSIS

POORLY DIFFERENTIATED - NO LONGER SEE PATTERN, NO LONGER SEE NUCLEAR FEATURES OF PTC, HAVE MITOSES INCLUDING ABNORMAL ONES AND NECROSIS.
HIGH GRADE AND POORLY DIFFERENTIATED THYROID CARCINOMA

POORLY DIFFERENTIATED CAN BE ASSOCIATED WITH BY HISTORY OR HISTOLOGY PTC, FVPTC, FTC or HCC.

(Presumably similar for high grade cancers.)
ANAPLASTIC THYROID CARCINOMA

- One of the most virulent cancers in humans
- Mortality of 90% at 6 months
- Can kill by local invasion +/- distant metastases
- By clinical and histological association, many if not most arise from lower grade cancers (papillary, follicular, Hurthle cell).
ANAPLASTIC CARCINOMA

- Elderly individuals usually over 60 years old
- Rare under 50 years old.
- Often large and extrathyroidal
- Makes up about 5% of thyroid cancer.
- Awful prognosis.
ANAPLASTIC THYROID CARCINOMA

- Common histological features:
  - Pleomorphic cells
  - Mitoses including abnormal forms
  - Necrosis
  - Vascular invasion
  - Extrathyroidal invasion
Cytopathology

- Morphologic patterns of ATC:
  - Spindle cell
  - Pleomorphic giant cell
  - Epithelioid/Squamoid

- Extensive necrosis

- In a series of 113 FNAs in patients with ATC:
  - 107 (94.7 percent) were diagnostic of malignancy
  - 96 of 107 were diagnosed as anaplastic thyroid cancer


The Bethesda System For Reporting Thyroid Cytopathology; Second Edition
ANAPLASTIC THYROID CARCINOMA

Patterns include:

- Spindle cell (can mimic sarcomas)
- Giant cells
- Squamous cell often with spindle cell features
- Can show rhabdoid cells
- Can mimic angiosarcoma
ANAPLASTIC THYROID CARCINOMA

Interesting pathologic findings:

Spindle squamous carcinoma arises in association with tall cell papillary carcinoma.

Tumor eosinophilia without serum eosinophilia can be seen (Secretion of eosinophil chemotactic factor).
Tall Cell Papillary Carcinoma
Tall Cell Papillary Carcinoma
Transition to an Anaplastic Spindle Cell Carcinoma
Anaplastic Spindle Cell Carcinoma
Anaplastic Spindle Cell Carcinoma
ANAPLASTIC CARCINOMA

- Arises as dedifferentiation of lowgrade lesion.

EVIDENCE:
- History
- Histology
- Molecular biology
ANAPLASTIC CARCINOMA

**HISTORY**

- Lowgrade lesion with recurrences and metastases
- Seen next to and admixed with lowgrade lesion
Transition to an Anaplastic Spindle Cell Carcinoma
ANAPLASTIC CARCINOMA

MOLECULAR BIOLOGY

The Braf story

- Braf mutations occur in 45% of papillary carcinoma - mostly classic and tall cell types
- Braf mutations in about 33% of anaplastic carcinoma.
ANAPLASTIC THYROID CARCINOMA

**MOLECULAR FEATURES**

- Can show Braf V600E mutation (if lower grade lesion does)
- Can show TERT mutations
- Can show p53 mutations
ANAPLASTIC CARCINOMA

**IMMUNOHISTOLOGY**
- Cytokeratin AE1/3, CK903, less Cam 5.2
- Thyroglobulin negative except diffusion
- TTF1 about 1/3 said to be +
- In squamous type, TTF1 positive in epithelial areas, not spindle cells.
- Helps distinguish with collision to head and neck squamous cancer.
- PAX 8 is also helpful: + in thyroid; negative in H&N squamous carcinoma
Cytokeratin AE 1/3 Immunohistochemistry

The papillary and anaplastic components positive for cytokeratin AE 1/3. Similar results with PAX 8
TTF-1 Immunohistochemistry

Note: Similar results seen for thyroglobulin
ANAPLASTIC CARCINOMA

- SPINDLE CELL SQUAMOUS CARCINOMA
  - Always from tall cell papillary carcinoma
  - May develop in recurrences or metastases or in primary site.
Three clinical scenarios for SSCC were identified:

- **Type I**: TCV with SSCC at the time of presentation: 19 patients;
- **Type II**: SSCC arising as a recurrence in patients with a known history of TCV: 4 patients;
- **Type III**: SSCC presenting like primary laryngeal SCC in a patient with or without a known history of TCV: 6 patients. TTF-1 and PAX 8 in squamous type, may help distinguish from collision tumor of PTC and SCC of head and neck origin.  

Gopal et al THYROID 2011.
ANAPLASTIC CARCINOMA

**PROGNOSIS**

- 90% dead of tumor in 6 months
- Rare survivals if found incidentally in thyroid or in metastasis.
- If patient survives question the diagnosis -- ???malignant lymphoma
- Remember: Paucicellular variant
ANAPLASTIC CARCINOMA

Interesting clinical scenario.

Transformation to anaplastic carcinoma occurs in metastatic sites with other metastases remaining as differentiated papillary carcinoma. The latter take up radioiodine and can be responsive to chemotherapy (kinase inhibitors) whereas anaplastic tumor is iodine refractory and may not respond to chemotherapy.
ANAPLASTIC CARCINOMA

Our recent experience with 3 cases

Site of Mets; bone (2); adrenal (1)

7 previously reported cases: sites of transformation all over.
## Anaplastic transformation of differentiated thyroid cancers at a metastatic site

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sex/age</th>
<th>Site of anaplastic transformation</th>
<th>Duration between primary diagnosis and anaplastic transformation (Y)</th>
<th>Histopathological features of anaplastic carcinoma</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotome et al.</td>
<td>F/82</td>
<td>Retroperitoneum</td>
<td>17</td>
<td>Spindle cell-type anaplastic carcinoma</td>
<td>Died</td>
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<tr>
<td>Takeshita et al.</td>
<td>F/81</td>
<td>Liver</td>
<td>5</td>
<td>Anaplastic carcinoma P53 mutated PTC</td>
<td>NA</td>
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<tr>
<td>Angeles et al.</td>
<td>F/58</td>
<td>Breast</td>
<td>20</td>
<td>Spindle and giant cell anaplastic carcinoma with rhabdoid inclusions PTC</td>
<td>NA</td>
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<tr>
<td>Al-Qsous et al.</td>
<td>M/83</td>
<td>Lung</td>
<td>10</td>
<td>Undifferentiated carcinoma PTC</td>
<td>Died</td>
</tr>
<tr>
<td>Kaushal et al.</td>
<td>F/52</td>
<td>Shoulder</td>
<td>8</td>
<td>Spindle cell-type anaplastic carcinoma PTC</td>
<td>Died 2 m after Dx</td>
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<tr>
<td>Nakayama et al.</td>
<td>F/55</td>
<td>Pelvis</td>
<td>12</td>
<td>Anaplastic carcinoma FTC</td>
<td>Died 2 m after Dx</td>
</tr>
<tr>
<td>Sugitani et al.</td>
<td>6 cases</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>48 days (median survival)</td>
</tr>
<tr>
<td>Abe et al.</td>
<td>M/61</td>
<td>Lung</td>
<td>10</td>
<td>Pleomorphic and undifferentiated anaplastic carcinoma PTC</td>
<td>Died 6 m after Dx</td>
</tr>
<tr>
<td>Solomon et al.</td>
<td>M/64</td>
<td>Retroperitoneum</td>
<td>30</td>
<td>Pleomorphic cells with rhabdoid features</td>
<td>Died 3 w after Dx</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>F/61</td>
<td>Lung and pleura</td>
<td>19</td>
<td>Anaplastic carcinoma with pleomorphic and spindle cell type</td>
<td>Died 4 m after Dx</td>
</tr>
<tr>
<td>Ambeilil et al.</td>
<td>F/76</td>
<td>Mandible</td>
<td>7</td>
<td>Spindle cell with large pleomorphic epithelial cells PTC, follicular variant</td>
<td>NA</td>
</tr>
</tbody>
</table>
ANAPLASTIC CARCINOMA

IS THERE ANY HOPE?

If anaplastic carcinoma is Braf mutated may have partial response to kinase inhibitors.

Some cases have been given drugs that decrease radiiodine resistance and make the tumors respond to that therapy.
ANAPLASTIC CARCINOMA

IS THERE ANY HOPE?

Not much yet but some trials with PDL1 inhibitors may show promise.
POORLY DIFFERENTIATED, HIGH GRADE AND ANAPLASTIC CARCINOMAS: WHAT IS EVERYONE TALKING ABOUT?