Outside the “well-differentiated thyroid carcinoma” box:

Problematic Thyroid Cases

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Case 1
Initial presentation at MDACC

- 36 year old male from Saudi Arabia
- CC: Lung masses
- HPI:
  - Had a thyroidectomy for mass 7 years prior
  - Outside pathology initially diagnosed as medullary thyroid carcinoma
  - This was revised to papillary thyroid carcinoma with “exuberant nodular fasciitis-like stroma”
  - Subsequently treated with I-131

Initial presentation (cont)

- Developed cough 6 years later
- Imaging studies ordered
  - Lung nodules
  - Thyroid bed recurrence
  - I-131 uptake negative
- Given additional I-131
- Referred to MDACC given persistent disease
Additional history

- Reports 8 lbs weight loss
- No chronic medical ailments otherwise
- No family history of thyroid cancer
- Smoking history, no radiation exposure

CT neck with contrast

- Multiple lung masses, bilateral.
- A large mass in the left thyroid bed (4.3 x 3.2 cm) and displaces the trachea to the right;
- Infiltrates the left tracheoesophageal groove, and involves the esophagus.
- Trachea is narrowed.
- Thyroglobulin is not elevated.

Lung core bx
Biphasic cell population

IHC

- Both cell types pan-keratin (+)
- Spindle cells smooth muscle actin (+)
- Epithelioid cells are EMA (+), focally PAX-8 (+)
- Negative for desmin and thyroglobulin
**Differential diagnosis:**

- PTC (spindle cell, nodular fasciitis variants)
- Medullary thyroid carcinoma
- Anaplastic thyroid carcinoma
- Sarcomatoid carcinoma
- Synovial sarcoma
- Spindle epithelial tumor with thymus-like elements
- Mesothelioma

**IHC**

- Tumor cells are negative for TTF-1, thyroglobulin, chromogranin, synaptophysin, calcitonin (MDACC)

**Diagnosis:**

*Spindle Epithelial Tumor with Thymus-like Differentiation- SETTLE*
SETTLE

- Coined by Chan & Rosai in 1991
- Encompasses previously described entities of “thyroid spindle cell tumor with mucous cysts” and some cases of malignant teratoma of thyroid

SETTLE Clinical Features

- Patients are young, mean age about 15yr
  - Congenital cases have been reported
- Equal sex distribution or possible slight male predominance
- Presents as a neck mass, occasionally with compression of surrounding structures
- 5 year survival 83-86%
  - Long term follow-up for metastases & recurrent disease

SETTLE Radiology/ Gross

- May be encapsulated, circumscribed, or infiltrative
- Majority occur in thyroid
- Metastases in 26% of patients
  - Lungs, lymph nodes, other viscera
SETTLE Histology

- Highly cellular, traversed by sclerotic bands
- Biphasic pattern with spindle cells closely associated with epithelial cells
  - Spindle cells are cytologically bland, with only few mitoses (<1 per 10 hpf)
  - Epithelial cells arrange in tubular/trabecular, papillary, sheet-like patterns
- Background stroma present and may have calcifications
- Histologically mimics synovial sarcoma with some exceptions:
  - Lower grade appearance of spindle cells
  - Absence of eosinophilic necrotic debris
  - Absence of stromal mast cells
SETTLE Immunohistochemistry

- HMW cytokeratin in both spindle and epithelial cells
- Scattered staining for LMW cytokeratin and EMA
- Frequently express CD99 and bcl-2 in both cell types, a minority express TLE1
- Membranous expression of CD117
- Negative for thyroglobulin, calcitonin, CK20, CD34
- Negative for SYT translocation
SETTLE Management

- Often managed with partial thyroidectomy
- Good outcomes with resections for metastases
- Responsive to chemotherapy and radiation

Medullary thyroid carcinoma

- Arise from C-cells
- 4% of all thyroid carcinoma
- 20% are hereditary
  - MEN 2, RET point mutations
- Serum calcitonin
  - Controversial on threshold values
  - Rare cases of MTC without calcitonin secretion
- FNA can be challenging
  - Aspirate calcitonin level may be a better tool
MTC- cont.

- May be multifocal
- Typically not encapsulated
- Usually in mid/upper portion of the gland
  Higher concentration of C-cells

Histology
- Round epithelioid cells, plasmacytoid
- Spindle cells
- Round nuclei with punctate chromatin
- Amyloid stroma
- C-cell hyperplasia

http://alf3.urz.unibas.ch/pathopic/e/getpic-fra.cfm?id=004853

http://alf3.urz.unibas.ch/pathopic/e/getpic-fra.cfm?id=003822
MTC Variants

Polymorphous entity:
- Follicular
- Papillary
- Oncocytic
- Small cell
- Giant cell
- Clear cell
- Squamous
- Melanotic
- Encapsulated
- Paraganglioma-like
PTC Variants

- Follicular
- Microcarcinoma
- Tall cell
- Oncocytic
- Columnar
- Diffuse sclerosing
- Solid
- Clear cell
- Cribiform morular (FAP)
- Macrofollicular
- With hobnail features
- With fasciitis-like stroma
- Combined with MTC
- With dedifferentiation to ATC

Papillary thyroid carcinoma with nodular fasciitis-like stroma

- Rarely reported entity, also first described in 1991
- Abundant stroma with cords of carcinoma
- Typical PTC nuclear features
- Typical PTC behavior

Bonus case

75 y/o man with thyroid nodule
Differential diagnosis

- MTC
- PTC
- ATC
- Metastatic carcinoma
IHC:

- Positive stains: TTF-1, thyroglobulin, CK, BRAF V600E
- Negative stains: calcitonin, synapto, S-100, Pan-Mel

Final diagnosis:

PTC, spindle cell variant

Primary spindle cell lesions

- Post–FNA spindle cell nodule
- Riedel thyroiditis
- Solitary fibrous tumor
- Muscle cell tumors
- Peripheral nerve sheath tumors
- Hyalinizing trabecular tumor
- SETTLE
- Carcinoma showing thymus-like differentiation (CASTLE)
- Follicular dendritic cell tumor
- Spindle cell variants of papillary, medullary, anaplastic, and squamous cell carcinoma
Anaplastic thyroid carcinoma

- Presents as rapidly enlarging neck mass
- Extremely aggressive with poor prognosis
- IHC:
  - Thyroglobulin<<TTF-1<<PAX-8

Case 2

53 yo female from China who presents with a thyroid nodule.

- She first sought medical care in 2012 because of hoarse voice and cough; was told that her R vocal cord was paralyzed.
- 2015- u/s which showed a R thyroid nodule that appeared benign and no bx; additional u/s in 2017-nodule decreased in size

Cont.

- 2018- bx thyroid nodule shows “poorly differentiated carcinoma” (MDACC FNA; PAX8 and TTF-1 both negative)
- TSH, T4, thyroglobulin- all normal
- No radiation exposure
- FNA of R supraclavicular LN: poorly differentiated carcinoma with squamous differentiation (p40+, focal synaptophysin, negative for TTF1, CD56, thyroglobulin, PAX8, NUT).
- NGS: no gene fusions, no CNVs, no somatic mutations
- Inferior aspect of R thyroid lobe - infiltrating mass, that extends into right tracheosophageal groove.
- Involvement of R tracheal wall, with intraluminal disease.
- R vocal cord paralyzed.
Differential diagnosis:

- Squamous cell carcinoma
- Anaplastic thyroid carcinoma
- Sarcomatoid carcinoma
- Medullary thyroid carcinoma
- SETTLE (spindled epithelial tumor with thymus-like elements)
- CASTLE (carcinoma showing with thymus-like elements)
Diagnosis:

CArcinoma Showing Thymus-Like differentiation (Elements)- CASTLE

CASTLE Clinical Presentation

- Rare
  - 0.08-0.15 % of thyroid malignant tumors
- Mean age 51
- Slight female predominance
- Presentation with neck mass or hoarseness

CASTLE Gross/ Radiology

- Hard lobulated mass
- Predominantly involves lower thyroid
- Rarely arises in perithyroidal soft tissues
CASTLE Histology

- Looks like thymic carcinoma or lymphoepithelial-like carcinoma
- Lobular groups of cells with pushing borders
- Fibrous bands, often with lymphoplasmacytic infiltrate
- Epithelial or spindle cells with ill-defined cytoplasm
- Vesicular nuclei and prominent nucleoli
- Does not have the pronounced necrosis seen in thymic carcinomas

CASTLE- IHC

Resembles thymic carcinoma

- Positive for cytokeratin (HMW, CK7), CD5+, p63, CD117, PAX-8, GLUT-1, bcl-2, EGFR
- Negative for TTF-1, thyroglobulin, calcitonin, vimentin, calretinin
- Rare positivity for neuroendocrine markers
- EBER negative
CASTLE Derivation

- Thymic derivation
  - Resemblance to thymic carcinoma
  - Vestigial thymus sometimes found in vicinity of CASTLE

- Ultimobrachial body remnants
  - Solid cell nests (SCN) also have been associated with CASTLE

CASTLE Prognosis/Management

- Good prognosis with 10 year survival of 82%.
- Nodal metastasis and tumor extension predict outcome.
- Primary resection with radiation has been suggested therapy

First address lesions relating to the thymus!

Neck tumors with thymic or branchial pouch differentiation

Four main types

1. Ectopic hamartomatous thymoma (EHT)
2. Ectopic cervical thymoma (ECT)
3. Spindle epithelial tumor with thymus-differentiation (SETTLE)
4. Carcinoma showing thymus-like differentiation (CASTLE)

Case 3

- 60 years old gentleman presenting to his pulmonologist for URI symptoms and SOB
- Treated with antibiotics, did not improve
- Seen by ENT, vocal cord paralysis
- CT neck 8.0 cm R thyroid mass
- R thyroid lobe mass displacing trachea to the left midline, with moderate luminal narrowing.
- Size: 7.8 x 4.6 x 3.8 cm.
- R vocal cord paralysis.
- Stable nonenlarged nodes in the inferior neck.
- 1.3 cm LN R internal jugular-FNA
- MDACC: high-grade neuroendocrine carcinoma (diffusely positive for synaptophysine, weak + for pan-keratin; negative for TTF1, PAX8, p40, chromogranin, BRAF V600E.

- En-block R thyroid lobectomy and isthmusectomy.
Differential Diagnosis

- Anaplastic (undifferentiated) thyroid carcinoma
- Medullary thyroid carcinoma
- Tumors with thymic-differentiation
- Lymphoma
- Primary extra-skeletal Ewing Sarcoma
Additional workup

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<tr>
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<tr>
<td>CD99</td>
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Final Diagnosis

Carcinoma Of The Thyroid With Ewing/ PNET Family Tumor Elements (CEFTE)

aka

Primary Extra-skeletal Ewing Sarcoma, Adamantinoma-like Variant

Key Features

- “Small blue cell tumor” with epithelial differentiation (p63+); good prognosis

Expression of CD99, EWSR1-FLI1 rearrangement

Eloy et al. USP 2014
Histogenesis

Hypothesis #1:
- Dedifferentiation of thyroid carcinoma; may co-exist with papillary thyroid carcinoma

Hypothesis #2:
- Thymic/branchial pouch remnants (solid cell nests)

Eloy et al. IJSP 2014

**EWSR1 translocation is seen ___% of papillary thyroid carcinoma?**

A. 0%
B. ~ 25%
C. ~ 50%

Case 4

- A 30 year-old woman presents with a 6.0 cm asymptomatic left thyroid lobe.
- FNA suggestive of Hürthle cell neoplasm.
- Underwent left thyroid lobectomy and isthmusectomy.
- Grossly, the entire lobe was replaced by a smooth, round and encapsulated mass, with residual rim of thyroid parenchyma.
H&E:

- Encapsulated high-grade malignant tumor with necrosis, mitotically active and variegated histological appearance.
- Squamous differentiation adjacent to reminiscent areas of differentiated follicular/Hürthle cell carcinoma.
- Neuroepithelial elements (similar to ependymal type rosettes).
- NO LVI, no ETE
IHC

The neuroepithelial component:

- Positive for cytokeratin, neurofilaments, and SALL4
- Negative for CD99, Calcitonin, synaptophysin, and chromogranin (excluding MTC)
- Lack of immunoreactivity for AFP, HCG, and CD30 r/o a germ-cell component.
Diagnosis

Malignant Thyroid Teratoma

The thyroid gland is accepted as site of origin for the teratoma if:

1. the tumor occupies a portion of the thyroid gland;
2. there is direct continuity between the tumor and the thyroid gland; or
3. the tumor has replaced the gland (no thyroid gland is identified intraoperative or by imaging.
4. a cervical teratoma was regarded to be of thyroid origin if normal tissue thyroid was found adjacent to or intermixed with tumor component.

Teratoma - malignant category

- Grade 3 immature teratomas (i.e., >4 low-power fields of immature neuroectodermal tissue, along with mitoses and cellular atypia)
- and/or the presence of embryonal carcinoma or yolk sac tumor
• All four patients were young women <40 years of age.
• One patient had thyroid surgery alone, another had surgery with postoperative adjuvant chemotherapy, and two patients underwent neoadjuvant chemotherapy with significant tumor regression prior to definitive thyroid surgery.

• No patients had postoperative radiation therapy.
• All patients remained alive and disease free a median of 172 months (range 52–282 months) following completion of therapy.
• neoadjuvant chemotherapy combined with surgical excision is a promising approach for patients with gross extrathyroidal extension, cervical lymph node metastases, and/or distantly metastatic disease.