Evening Specialty Conference: Cytopathology

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Dr. N. Paul Ohori declares he has no conflict of interest to disclose.

Clinical History: A 71 year old woman presented with hoarseness and dyspnea. Biopsy of a tracheal mass and FNA of a cervical lymph node showed a carcinoma with ETV6/NTRK3 gene fusion. In addition, a 4.6 cm left thyroid mass and a 2.6 cm right thyroid mass were identified. FNA of the left thyroid mass was performed.
What is the significance of ETV6/NTRK3 gene fusion?

ETV6/NTRK3 gene fusion

- Fusion of ETS variant 6 gene on chromosome 12 to the neurotrophic tyrosine receptor kinase 3 gene on chromosome 15.
- The resulting transcript encodes for a chimeric protein product that is a constitutively active tyrosine kinase.
- ETV6/NTRK3 gene fusion has been found in a variety of neoplasms.

Neoplasms with ETV6/NTRK3 gene fusion

- Infantile (Congenital) Fibrosarcoma (1998)
- Congenital Mesoblastic Nephroma (1998)
- Acute Myeloid Leukemia (1999)
- Secretory Breast Carcinoma (2002)
- Chronic Eosinophilic Leukemia (2011)
- Inflammatory Myofibroblastic Tumor (ALK-negative) (2016)

Neoplasms with ETV6/NTRK3 gene fusion

- Mammary Analogue Secretory Carcinoma (MASC) (2010)
  - Salivary gland MASC
    - Parotid
    - Submandibular
    - Minor
  - Skin MASC
  - Thyroid MASC (2015)
- Papillary Thyroid Carcinoma with ETV6/NTRK3 gene fusion (2014)

Differential Diagnosis

- Salivary gland MASC
- Thyroid MASC
- Papillary Thyroid Carcinoma
- Metastasis from other neoplasms with ETV6/NTRK3
Previous Specimens

- Tracheal biopsy (1 month prior)
  - Carcinoma with *ETV6/NTRK3*
- Lymph Node FNA (2 weeks prior)
  - Carcinoma

Other immunohistochemistry results:
- Positive – PanCK, CK7, CK5/6, GCDFP (focal), Mammaglobin (focal)
- Negative – S100, ER, p63, Calponin, Napsin-A, CK20, p53, WT-1

Tracheal Biopsy: Carcinoma with *ETV6/NTRK3*

- PAX-8
- TTF-1

Lymph Node FNA: Carcinoma

- Mammaglobin
- GCDFP-15

PAX-8

Mammaglobin
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Differential Diagnosis based on Tracheal Biopsy and Lymph Node FNA

- Carcinoma in tracheal biopsy and lymph node FNA sample with similar morphologic features.
- PAX-8 positive
- TTF-1 negative
- GCDFP/Mammaglobin positive

- Differential Diagnosis:
  - Papillary Thyroid Carcinoma (favored diagnosis)
  - MASC (salivary gland vs thyroid)

Back to our index case:

- Left Thyroid FNA
  - Cytopathology Diagnosis: Papillary Thyroid Carcinoma
  - [No cell block available for IHC]
  - Molecular Studies (ThyroSeq): ETV6/NTRK3

Cytology and Molecular Test Summary

- Tracheal biopsy: Carcinoma with ETV6/NTRK3 (with DDx)
- Lymph Node FNA: Carcinoma (with DDx)
- Left Thyroid FNA: PTC with ETV6/NTRK3

- Tracheal biopsy, lymph node biopsy, and thyroid FNA specimens with shared features.
- Involved with the same gene fusion.
- Is all of this Papillary Thyroid Carcinoma with ETV6/NTRK3?

Salivary Gland MASC

- Skalova (2010): Mammary Analogue Secretory Carcinoma (~Sec Br Ca)
- Tubular, microcystic, and solid patterns – may mimic thyroid carcinoma
- In salivary glands, ETV6/NTRK3 (12;15) (p13;q25) is specific for MASC.
- Other fusion partners discovered - ETV6-X
- Prior “MASC” Dx - Zymogen-poor Acinic Cell Carcinoma or ADC, NOS.
- Positive IHC: Mammaglobin, GCDFP, S100, GATA-3, CK7, CK19, DOG-1
- Negative IHC: Calponin, SMA, p63, CK5/6
- High-grade MASC: necrosis, prominent nucleoli and pleomorphism
- Low-grade MASC: may mimic Salivary Gland Adenoma
- Prognosis: overall 44-92 mo DFS; high-grade – 24-72 mo DOD.

What have we learned about Head and Neck carcinomas with ETV6/NTRK3 gene fusion recently?

**Thyroid MASC**

- Histology, IHC, and Molecular features ~ Salivary gland MASC
- Positive IHC: Mammaglobin, GCDFP, S100, p63, GATA-3, weak PAX-8
- Negative IHC: TTF-1, Thyroglobulin
- Large, infiltrative, extra-thyroidal extension, locally aggressive – can invade into trachea, high stage
- May be associated with synchronous PTC
- Frequent recurrence but associated with long term survival
- Role of Tyrosine kinase inhibitors (TKI) (e.g. entrectinib)

**Metastasis from other carcinomas with ETV6/NTRK3**

- Secretory Breast Carcinoma (SBC)
  - Tubular, micropapillary, solid patterns, intra and extracellular eosinophilic secretions
  - Usually low-grade with mild to moderate nuclear atypia
  - Occasional high-grade SBC with numerous mitoses and necrosis
  - Triple-negative breast carcinoma
  - ETV6/NTRK3 is specific for SBC in the breast
  - In the current case, breast carcinoma was excluded by negative imaging studies.

**Papillary Thyroid Carcinoma with ETV6/NTRK3**

- ETV6/NTRK3 is the second most common genetic alteration in radiation-related thyroid carcinoma ~14% (after RET/PTC).
- ~1-2% among sporadic well-differentiated PTCs (higher in pediatric population).
- Rad associated: FVPTC or Classic PTC +/- solid growth pattern
- Non-rad associated:
  - Mixed follicular and papillary patterns
  - (occ pure Classic or FVPTC)
  - Infiltrative and multinodular
  - Clear cell or oncocytic features
  - Cytoplasmic vacuoles (similar to MASC)
  - Locally aggressive, can metastasize
  - Lymph node metastasis
  - Psammoma bodies
  - Overt nuclear features of PTC

**Tracheal Resection (2 months after index case)**

- Left Neck Dissection
- Total Thyroidectomy
Pertinent Issues for the Thyroid FNA case
- MASC has many masks
- *ETV6/NTRK3* is a specific marker in the appropriate context.
  - More helpful with single organ involvement (e.g. salivary gland).
  - More complicated with thyroid gland involvement.
- High-grade MASC
  - vs “higher grade” transformation of PTC.
  - May mask the typical morphologic features of MASC.
- Therapeutic implications
  - High stage PTC/MASC treated with surgery and/or chemotherapy/radiation
  - TKI (e.g. entrectinib)
  - Acquired resistance (*NTRK3 G623R* mutation)

Summary
- Tracheal biopsy (1 month prior)
  - Carcinoma with *ETV6/NTRK3*
- Lymph Node FNA (2 weeks prior)
  - Carcinoma (similar to tracheal biopsy)
- Left Thyroid FNA (index case)
  - “Papillary Thyroid Carcinoma” with *ETV6/NTRK3*
- Tracheal Resection
  - MASC with LN metastasis and extension into Thyroid
Message 1

**ETV6/NTRK3** gene fusion is found in a variety of neoplasms
- Infantile (Congenital) Fibrosarcoma (1998)
- Congenital Mesoblastic Nephroma (1998)
- Acute Myeloid Leukemia (1999)
- Secretory Breast Carcinoma (2002)
- *Mammary Analogue Secretory Carcinoma (MASC)* (2010)
- Chronic Eosinophilic Leukemia (2011)
- *Papillary Thyroid Carcinoma* (2014)
- Inflammatory Myofibroblastic Tumor (ALK-negative) (2016)

Message 2

**MASC** can mimic Papillary Thyroid Carcinoma with **ETV6/NTRK3** gene fusion
- Distinguishing features:
  - Cyto-histologic features
  - Mammaglobin, GCDFP, DOG-1, TTF-1, Thyroglobulin
- MASC with high-grade transformation may mask characteristic features
- Solid pattern with high-grade nuclear features may be from MASC or PTC
- Sometimes, you will not know until it comes out.

Message 3

Most MASCs are indolent although some may behave aggressively.
- Most are comparable to other low-grade salivary gland carcinomas.
- High stage MASC treated by chemotherapy/radiation
- Therapeutic implications of **ETV6/NTRK3** gene fusion
  - (TKI e.g. entrectinib)

References


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