Head, Neck and Endocrine Specialty Conference

USCAP 2016

Lori A. Erickson, M.D.

Mayo Clinic

Rochester, MN, USA

(Nothing to Declare)
Clinical History

81 year old female with 2.2 cm mass right lobe of thyroid
Immunophenotype

• **Positive**
  – Cam5.2
  – Cytokeratin 7
  – Chromogranin
  – Synaptophysin
  – Calcitonin
  – TTF1
  – CEA

• **Negative**
  – Thyroglobulin
Diagnosis

Medullary thyroid carcinoma with papillary growth pattern
Medullary Thyroid Carcinoma

• 5-8% of thyroid carcinoma

• Most sporadic, 25% autosomal dominant

• MEN 2A, Familial MTC, MEN 2B
  – MEN 2A: early adult
  – Familial MTC: older than others
  – MEN 2B: often young (infants & children)

• MTC can have unusual histologic features difficult to recognize as MTC
Medullary Thyroid Carcinoma
Analysis of Amyloid in Medullary Thyroid Carcinoma by Mass Spectrometry Based Proteomic Analysis

Erickson et al Endocrine Pathology 2015

- 9 MTC (1 MEN2A, 1 familial MTC, and 7 sporadic)

- Sampling by laser microdissection and tandem mass spectrometry based proteomic analysis -> spectra are compared with canonical protein sequence databases, filtered and identified with software indicating the specific peptides & associated proteins

- Calcitonin showed complete coverage
MTC: Spindle
MTC: Follicular pattern
MTC: Follicular pattern
Medullary Thyroid Carcinoma (MTC)

Hyalinizing trabecular tumor-like

MTC: Hyalinizing trabecular tumor-like
Thyroid Paraganglioma

MTC: Paraganglioma-like
MTC: Papillary pattern
MTC: Papillary pattern
MTC: Intranuclear Pink Holes
MTC: Hurthle/oxyphilic
MTC: Cytoplasmic clearing
MTC: Necrosis
MTC: Pleomorphic (giant cell)
Small Follicles
Mixed with Larger
Thyroglobulin
Chromogranin
Other Histologic Variants of MTC

• Squamous change
• Mucin: 40% extracellular, 15% intracellular
• Melanin: rare, single cells
• Small cell variant MTC: small cell lung cancers
  – Worse prognosis than typical MTC
  – +/- Calcitonin
  – + CEA & calcitonin gene related peptide
Medullary Microcarcinoma (≤1cm)

Familial (vs sporadic)

- Bilateral 68.8% (vs 8.8%)
- Multifocal 81.3% (vs 8.8%)
- C-cell hyperplasia 100% (vs 71%)

(AJSP, 2001. 25:1245-51)

LN metastases: extrathyroid extension, multifocal, size, desmoplastic stroma

- 37% (65 of 176) with LN removed had metastases
- 23% tumors ≤5 mm LN metastases (more >5 mm)
Syndrome Associated MTC (25% of MTC)

- Bilateral, multifocal, C-cell hyperplasia: nonspecific
- Germline RET mutation analysis recommended for patients with MTC
- Virtually all familial MTC (MEN2A, MEN2B, FMTC) have RET germline mutation
  - >100 mutations, duplication, insertion or deletion
- RET encodes transmembrane receptor tyrosine kinase involved in cell signaling pathways
Sporadic MTC

• 60% somatic RET mutation
  – M918T (11-60%): aggressive?, tumor size
  – Rare: 618, 603, 634, 768, 804, 883, partial deletion RET

• 12-80% sporadic MTC w/o RET mutation have RAS mutation
  – H-RAS (56%), K-RAS (12%), rarely NRAS

(Wells Clin Endo Metab 2013; Santoro Endocr 2004; Santoro Cold Spring Harb Persp Biol. 2013)
Classical MEN2A

- 95% exon 11 (codon 634) or exon 10 (609, 611, 618, 620)
- MTC 100%
- PHEO 30-50% benign, bilateral, 634 (less exon 10)
- Diffuse nodular adrenal medullary hyperplasia: 918, 634
- Hyperparathyroidism: mild, 1-4 glands
  - Codon 634 (30% penetrance); 609, 611, 618, 620 (2-12%)
MEN2A

- **MEN2A & Cutaneous Lichen Amyloidosis**
  - 634
  - Usually sporadic, can be hereditary, back T2-6

- **MEN2A & Hirschsprung Disease**
  - 609, 611, 618, 620
  - 7% MEN2A have HD, 2-5% HD have MEN2A
  - *RET* mutation 50% hereditary HD & 15-20% sporadic HD

- **Familial Isolated MTC**: no PHEOs or HPTH
MEN2B

- Present infancy, aggressive, metastasize early
- MTC (100%), PHEOs (50%), marfanoid habitus, typical facies, ganglioneuromas
- 75% de novo RET mutation, 25% known familial
- 95% point mutation codon M918T (exon 16)
- <5% exon 15 A883F (less aggressive)
- Atypical MEN2B: rare, 20-30 years
  - Double RET germline mutations codon V804M and either Y806C, S904C, E805K or Q781R

## American Thyroid Association Risk Categories

<table>
<thead>
<tr>
<th>2015</th>
<th>2009</th>
<th>RET codon</th>
<th>Thyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Highest Risk” ATA-HST</td>
<td>D</td>
<td>M918T</td>
<td>Immediately, children 1\textsuperscript{st} months life, PHEO screen 11Y</td>
</tr>
<tr>
<td>“High Risk” ATA-H</td>
<td>C</td>
<td>C634, A883F</td>
<td>&lt; 5 years old, PHEO screen 11Y</td>
</tr>
<tr>
<td>“Moderate Risk” ATA-MOD</td>
<td>A &amp; B</td>
<td>Mutations other than M918T, C634, and A883F</td>
<td>&lt; 5 years or later if screen calcitonin each 6 months, PHEO screen 16 Y</td>
</tr>
</tbody>
</table>

Wells et al. Thyroid 2015;25:567-610
- Junction between upper 1/3 & lower 2/3 lateral lobes
- Ultimobranchial bodies migrate from neural crest, become entrapped upper and middle poles of thyroid and give rise to C-cells
MTC Treatment & Prognosis

• Surgery: thyroidectomy, central compartment LN
• Not take up radioactive iodine, radioresistant
• Tyrosine kinase inhibitors targeting RET & VEGFR
  – 2011 FDA Vandetanib: TKI of RET, VEGFR2, VEGFR3, EGFR
  – 2012 Cabozantinib: TKI of RET, MET, VEGFR2
  – Increased PFS, but resistance develops
• Familial tumors diagnosed by biochemical or molecular methods better prognosis & miR-224
• Worse: older, male, present clinical (vs molecular), higher TNM, sporadic (vs hereditary), less extensive surgery, and possibly miR-183 & miR-375
Summary: MTC

- Be alert to the unusual variants of MTC
  - Immunostain panel - helpful unusual variants
- 25% syndromic (MEN 2A, 2B, Familial MTC)
- \textit{RET} mutation (also used to screen relatives)