C Cell Hyperplasia and Medullary Thyroid Carcinoma

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Thyroid Carcinoma

Most rapidly increase incidence of human cancer
- 7th most common tumor in women
  - 1980: 10,000
  - 2004: 23,600
  - 2006: 30,180
  - 2011: 48,020
  - 2015: 62,450

Thyroid cancer represents 3.8% of all new cancer cases in the U.S
- About 1,950 people estimated to died of thyroid cancer in 2015 in the US

SEER
Figure 1.7

Trends in SEER Incidence Rates by Sex and Primary Cancer Site
2003-2012

All Races, Males

- Thyroid: -5.1%
- Liver & Intrahepatic Bile Duct: -1.0%
- Melanoma of the Skin: 0.0%
- Kidney & Renal Pelvis: 1.5%
- Myeloma: 0.6%
- Pancreas: 0.6%
- Testis: 0.5%
- Oral Cavity & Pharynx: 0.5%
- Leukemia: 0.0%
- Non-Hodgkin Lymphoma: 0.2%
- Brain & Other Nervous System: -0.4%
- Hodgkin Lymphoma: -0.9%
- Esophagus: -1.0%
- Urinary Bladder: -1.0%
- All Sites Except Lung: -1.2%
- All Cancer Sites: -1.3%
- Stomach: -1.4%
- Larynx: -2.0%
- Lung & Bronchus: -2.6%
- Prostate: -2.9%
- Colon & Rectum: -3.1%

All Races, Females

- Thyroid: -5.5%
- Liver & Intrahepatic Bile Duct: 1.0%
- Corpus & Uterus, NOS: 1.6%
- Kidney & Renal Pelvis: 1.3%
- Myeloma: 0.8%
- Melanoma of the Skin: 0.7%
- Pancreas: 0.6%
- Leukemia: 0.3%
- Oral Cavity & Pharynx: 0.2%
- All Sites Except Lung: 0.1%
- Breast: 0.1%
- All Cancer Sites: -0.1%
- Non-Hodgkin Lymphoma: -0.5%
- Stomach: -0.7%
- Brain & Other Nervous System: -0.8%
- Hodgkin Lymphoma: 0.8%
- Lung & Bronchus: 4.2%
- Urinary Bladder: -1.3%
- Cervix Uteri: -4.5%
- Ovary*: -1.6%
- Larynx: -1.9%
- Esophagus: -2.4%
- Colon & Rectum: 0.9%

Annual Percent Change, 2003-2012

Source: SEER 18 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG).
Underlying rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1163).
For sex-specific cancer sites, the population was limited to the population of the appropriate sex.
* The APC is significantly different from zero (p<.05).
* Ovary excludes borderline cases or histologies 8442, 8451, 8462, 8472, and 8473.
5-year survival rate

- Localized: 99.9%
- Regional: 97.8%
- Distant: 54.1%
- Unstaged: 87.7%

Age distribution:

- <20: 1.8%
- 20-34: 15.1%
- 35-44: 19.4%
- 45-54: 24.1%
- 55-64: 20.1%
- 65-74: 12.6%
- 75-84: 5.6%
- >84: 1.4%
Thyroid Carcinoma

• **Derived from follicular cells - ~90-95% thyroid tumors**
  – Papillary thyroid carcinoma: ~80-85%
  – Follicular carcinoma: ~10%
  – Poorly differentiated carcinoma: ~1%
  – Anaplastic carcinoma: ~1%

• **Derived from calcitonin-producing C cells: ~5-10% of thyroid malignancies**
  – Medullary thyroid carcinoma

• **Other tumors:**
  – Squamous cell carcinoma, CASTLE, SETTLE
Medullary Thyroid Carcinoma

C cells
Case 1: 28 year old man with markedly enlarged thyroid and multiple enlarged LNs
MTC - FNA
Medullary Thyroid Carcinoma

Calcitonin
Medullary Thyroid Carcinoma

- Medullary carcinoma of thyroid is a malignant tumor showing C cell differentiation
- A well recognized familial predisposition to medullary thyroid carcinoma (MTC) in ~25% of cases
  - MEN 2A and 2B
  - Familial Medullary Thyroid Carcinoma (FMTC)
- Most located in the mid portions of the lobe corresponding to the C cell predominance
- Progression from C cell hyperplasia to carcinoma
  - Known RET gene mutation
C Cells

- C cells are second type of endocrine cells in the thyroid
  - Secrete calcitonin
  - Endodermal in origin
  - Make <0.1 % mass of the thyroid

- Normally present at the junction of upper and middle third of lateral lobe of thyroid
C-cell Distribution
C Cells

• Large clear cells (larger than normal follicular cells) with a central nucleus with fine chromatin in a peri- or para-follicular location

• Immunohistochemical staining:
  – Calcitonin
  – Neuroendocrine markers
  – CEA
Normal Adult C-cells
C-cell Topography

A

B

C

D
C Cells and Solid Cell Nests

Often in association with solid cell rests, a remnant of ultimobranchial body.
C Cell Hyperplasia
C Cell Hyperplasia

• First described in early 1970s

• Definition of hyperplasia is still controversial:
  1. Group of cells larger than 20 cells
  2. >50 cells in one low power field (x100)

• Serologically patients with C cell hyperplasia show increased levels of Calcitonin
C Cell Hyperplasia

Physiologic or Reactive Hyperplasia:

• Metabolic (hypercalcemia)
• Inflammatory and autoimmune diseases (Hashimoto's thyroiditis)
• Adjacent to masses (goiters, adenomas, other non-medullary neoplasms)
  • Hypergastrenemia
• Drugs (cimetidine, estrogens)
• After partial removal of thyroid
  • Old age
C Cell Hyperplasia
Diffuse or Nodular
C Cell Hyperplasia

Neoplastic C cell hyperplasia:

• Seen in the setting of certain familial diseases
  - MEN 2A and 2B (associated with specific mutations in \textit{RET} oncogene (exon 10,11,16)
• In familial settings the hyperplasia is precursor of medullary carcinoma of thyroid
C Cell Hyperplasia

– “Neoplastic” C cell hyperplasia: \textit{RET} mutation, associated with heritable MTC

– “Reactive” C cell hyperplasia: non-heritable:
  - Ageing
  - Hyperparathyroidism
  - Hypergastrinemia
  - Lymphocytic thyroiditis
  - Adjacent to follicular tumors
Nodular C cell hyperplasia:
Difficult to separate from medullary microcarcinoma

Histological features which can be helpful in making such distinction:
- Small nuclear size, pale cytoplasm and an intact basement membrane (seen using PAS stain or Collagen IV stain) favors a hyperplastic focus
# Physiologic vs. Neoplastic CCH

<table>
<thead>
<tr>
<th>Feature</th>
<th>Physiologic CCH</th>
<th>Neoplastic CCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable on H&amp;E stains</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Seen adjacent to MTC</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bilaterality</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Staining with NCAM</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Calcitonin reactivity</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Is C-cell Hyperplasia Really Hyperplasia?

C-cell hyperplasia is a clonal process and most likely represents a preinvasive malignancy (C-cell carcinoma *in situ*)
Differential Diagnosis of C-cell Hyperplasia

Tangential cut of follicles
Palpation thyroiditis
Intrathyroidal parathyroid tissue
Solid cell nests
Metastatic neoplasm
Medullary Thyroid Microcarcinoma
Micro MTC
Medullary Thyroid Microcarcinoma

Less than 1 cm

Sporadic or familial

Incidental finding in patients undergoing thyroidectomies for nodular thyroid disease

Detected by routine calcitonin screening in patients with nodular thyroid disease

In prophylactic thyroidectomies
# Sporadic vs. Familial Micro MTC

<table>
<thead>
<tr>
<th></th>
<th>Sporadic</th>
<th>Familial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multifocality</td>
<td>Rare</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Bilaterality</td>
<td>Rare</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Physiologic CCH</td>
<td>Majority</td>
<td>Rare</td>
</tr>
<tr>
<td>Neoplastic CCH</td>
<td>Rare</td>
<td>Majority</td>
</tr>
</tbody>
</table>
Sporadic MTC
Medullary Thyroid Carcinoma

Gross Features

- Typically at the junction of upper and middle third of lobe
- Well circumscribed
- Firm, gray-yellow, gritty cut surface
- Small to very large
Sporadic Medullary Thyroid Carcinoma
Familial MTC (Bilateral Tumors)
Medullary Thyroid Carcinoma

• **Sporadic:** mean age 50 years, unilateral

• **Familial:** bilateral, C cell hyperplasia

1. **FMTC:** not associated with other endocrinopathies; mean age 50 years

2. **MEN 2A:** late adolescence or early adulthood up to mid 30’s

3. **MEN 2B:** infancy or early childhood
Medullary Thyroid Carcinoma

- Histologic appearance quite variable
- Round, polygonal, spindle-shaped
- Clear, amphophilic, or eosinophilic cytoplasm
- Round to oval nuclei
- Neuroendocrine-type chromatin
Medullary Thyroid Carcinoma
Medullary Thyroid Carcinoma

Immunohistochemistry:

- Chromogranin
- Synaptophysin
- Calcitonin
- CEA
- TTF1
- LMW keratin
- PR
- S100
Molecular Evidence of Medullary Thyroid Carcinoma

- **1987** - genetic defect causing MEN2A located in chromosome 10
- **1993** - MEN2A and FMTC caused by germline RET mutations
- **1996** - MEN2B also caused by germline RET mutations
- **1996** - somatic RET mutations were detected in 40-50% of sporadic MTC
Ret gene (exons 1~20)

Cysteine-rich domain

Trans-membrane domain

Intracellular tyrosine kinase domains

ret-ptc breakpoint region

609,611 618,620
609,611
618,620

630,634
634

768,790 791 790
804 804
891 883
918 918

RET mutations in MTC Disease phenotype correlates strongly with mutations in specific codons of RET

- Familial MTC
- MEN 2A
- MEN 2B
- Sporadic MTC
Effect of a Somatic Codon 918 $RET$ Mutation on Survival in Sporadic MTC

Cumulative Percent Surviving

$P = 0.07$

Survival Time (Years)
MEN2: Familial Medullary Thyroid Carcinoma

3 Syndromes: MEN2A, MEN2B, and FMTC
<table>
<thead>
<tr>
<th></th>
<th>FMTC</th>
<th>MEN 2A</th>
<th>MEN 2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary Thyroid Carcinoma</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>C Cell Hyperplasia</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>0</td>
<td>10-60</td>
<td>50</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>0</td>
<td>10-30</td>
<td>0</td>
</tr>
<tr>
<td>Marfanoid habitus</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Int. ganglioneuromatosis</td>
<td>0</td>
<td>0</td>
<td>60-90</td>
</tr>
<tr>
<td>Mucosal neuromas</td>
<td>0</td>
<td>0</td>
<td>70-100</td>
</tr>
<tr>
<td>Thick corneal nerves</td>
<td>0</td>
<td>rare</td>
<td>60-90</td>
</tr>
</tbody>
</table>
Multiple Endocrine Neoplasia 2B

- **Mucosal neuromas**
  - Lips, tongue, buccal mucosa, +/- conjunctivae, eyelids and corneas

- **Ganglioneuromas**
# Familial Medullary Thyroid Carcinoma (FMTC)

<table>
<thead>
<tr>
<th>Age at diagnosis of MTC</th>
<th>MEN2B</th>
<th>MEN2A</th>
<th>Familial Medullary Thyroid Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy to &lt;5 years</td>
<td>&lt;35 years</td>
<td>~50 years</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>Most develop medullary carcinoma</td>
<td>&gt;90% develop medullary carcinoma</td>
<td>100% develop medullary carcinoma</td>
</tr>
<tr>
<td>Presentation</td>
<td>Aggressive form; preventable by prophylactic thyroidectomy</td>
<td>Up to 70% have already lymph nodes metastases at time of diagnosis</td>
<td>Medullary carcinoma is the only neoplasm</td>
</tr>
<tr>
<td>% of MEN2 Syndromes</td>
<td>~5%</td>
<td>~70-80%</td>
<td>~10-20%</td>
</tr>
</tbody>
</table>
MEN2
## Features Distinguishing Sporadic from Familial Medullary Thyroid Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Sporadic</th>
<th>Familial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laterality</strong></td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td>Solitary</td>
<td>Multicentric</td>
</tr>
<tr>
<td><strong>Associated with C cell hyperplasia</strong></td>
<td>No/unknown</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Neoplastic C cell hyperplasia</strong></td>
<td>Rare</td>
<td>Frequent (~100%)</td>
</tr>
<tr>
<td><strong>Lymph nodes metastases at time of diagnosis</strong></td>
<td>Usually present</td>
<td>May be present</td>
</tr>
</tbody>
</table>
Management of MEN 2 and FMTC Patients According to the RET Phenotypes

<table>
<thead>
<tr>
<th>Codons</th>
<th>Thyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>883, 918</td>
<td>Less than 1 year; within first 6 months</td>
</tr>
<tr>
<td>609, 611, 618, 620, 630, 634, 912</td>
<td>Before 5 years of age</td>
</tr>
<tr>
<td>533, 649, 666, 768, 790, 791, 804, 891</td>
<td>Between 5-10 years of age</td>
</tr>
</tbody>
</table>
Familial Medullary Thyroid Carcinoma
A Practical Approach

• **Thyroid pathology:**
  – Multiple tumors
  – Bilateral tumors
  – Associated with C cell hyperplasia
  – Lymph node metastases

• **Critical role of the pathologist in the identification of a familial setting**

• **Calcitonin immunostain must be performed to evaluate for C cell hyperplasia!**
Medullary Thyroid Carcinoma

Differential Diagnosis

- Follicular Carcinoma
- Undifferentiated Carcinoma
- Papillary Thyroid Carcinoma
- Hyalinizing Trabecular Tumor
  - Paraganglioma
- Other Neuroendocrine Tumors
  - Melanoma
Familial Medullary Thyroid Carcinoma
Useful Pathological Criteria

• Thyroid pathology:
  – Multiple tumors
  – Bilateral tumors
  – Associated with C cell hyperplasia
  – Lymph node metastases
Familial Medullary Thyroid Carcinoma
In the identification of a familial setting

What we will need to do:
• Calcitonin immunostain must be performed in both superior-mid lobes to evaluate for C cell hyperplasia

• Submit entire superior-mid poles of both lobes in all prophylactic thyroidectomies and perform calcitonin immunostaining
History

• 2004: 50-year-old woman with history of right quadrant abdominal pain diagnosed with metastatic neuroendocrine carcinoma in liver (on biopsy) and with bony disease

• Right colectomy: Ileal diverticulitis, right-sided diverticular disease. No evidence of a primary carcinoid tumor
History

• 2007: A large fibroid (11 cm) with right-sided adnexal cyst measuring 1.9 x 1.9 cm

• 2008: Total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic lymphadenectomy and omentectomy
Inhibin
Diagnosis

- Left Fallopian tube and Ovary: Metastatic well-differentiated neuroendocrine tumor, 4.5 cm
- Right Fallopian tube and ovary: Metastatic well-differentiated neuroendocrine tumor, 4.0 cm
- Tumor not present on the ovarian surfaces
- IHC: Positive: Chromogranin, synaptophysin, CAM5.2, Inhibin (focal)
Follow Up

- Dec 2008: Neck mass
  - FNA: Thyroid (Right middle pole)
    - POSITIVE FOR MALIGNANT CELLS
    - Positive: Calcitonin and TTF-1 (weakly)
    - Consistent with medullary thyroid carcinoma
- Serum calcitonin level: 15,324 pg/ml
- Suspicion of metastatic neuroendocrine carcinoma being medullary thyroid carcinoma
Diagnosis

• Jan 09: Total Thyroidectomy
  - Medullary thyroid carcinoma, multifocal, epithelioid variant with extensive amyloid deposition, right lobe (3.5 mid and upper pole and 0.9 cm lower pole)
    - No C cell hyperplasia
  - One lymph node at isthmus, positive for tumor

• Ovarian tumor reviewed
The ovarian tumor was stained for TTF-1 and Calcitonin and was found to be positive consistent with metastatic medullary carcinoma thyroid.
Discussion

• Medullary carcinoma of thyroid is a malignant tumor showing C cell differentiation (5-10% of all thyroid malignancies)
  • Most tumors are sporadic

• 20-25% are heritable
  - MEN 2A and 2B
  - Familial Medullary Thyroid Carcinoma (FMTC)

• Most located in the mid portions of the lobe corresponding to the C cell predominance
• In familial setting hyperplasia of C cell is a precursor lesion
Discussion

• Clinical presentation:
  - Mass lesions +/- pain
  - Hoarseness of voice
  - Almost all produce Calcitonin, rarely Cushing syndrome
  - Usual sites for distant metastasis are liver, lung, bone, brain and soft tissue

• Metastasis accounts for 21% of all ovarian malignancies
  • Thyroid carcinoma is an uncommon primary site most being PTCs
  • Medullary carcinoma metastasizing to ovary is extremely rare
Discussion

• Only two case reports:

1. A MEN 2 patient with a medullary carcinoma subsequently developed a metastasis to ovary

2. Patient first presented with an adnexal mass diagnosed as metastatic neuroendocrine carcinoma and 3 months later came back with a neck mass which was found to be a medullary thyroid carcinoma
...To Remember...

• Medullary thyroid carcinoma should be kept in mind as a primary site in cases presenting with metastatic neuroendocrine carcinomas

• Immunohistochemical staining including a panel of neuroendocrine markers and calcitonin should be performed in difficult cases

• Rarely mimic sex cord tumours of the ovary - therefore a sex cord markers should also be included in the panel
References


