Medullary Thyroid Cancer

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Grand Rounds Presentation
October 27, 2010
The Basics

- Malignant neoplasm of the parafollicular C-cells of the thyroid

- Neuroendocrine tumor
  - Parafollicular cells are of neural crest origin

- 3rd most common thyroid cancer
  - 4% of all thyroid cancers
  - 1000 new cases each year

- Secretory tumor
  - Calcitonin (most common)
  - Carcinoembryonic antigen (CEA)
  - ACTH, Substance P, Gastrin

- Two types
  - Sporadic
  - Familial
Presentation

- Slow growing neck mass
- 50-60% nodal involvement when detected
- Compressive symptoms (dyspnea, dysphagia)
- Hoarseness (RLN)
- Paraneoplastic syndromes
  - Cushing’s, Carcinoid
- Diarrhea
  - Calcitonin causes increased secretion of electrolytes into the intestine
Sporadic vs. Familial

- **Sporadic**
  - 75% of MTC cases
  - Unifocal and unilateral
  - Age at presentation: 5-6\textsuperscript{th} decade
  - No family history
  - Worse prognosis
Sporadic vs. Familial

- **Familial**
  - 25% of MTC cases
  - Multifocal and bilateral
  - Autosomal dominant association
    - MEN IIA/IIB
    - Familial MTC
  - RET proto-oncogene mutation on chromosome 10
    - Codes for a tyrosine kinase receptor protein
  - Age at presentation: 2nd - 3rd decade
  - Better prognosis (found earlier)
  - Progression
    - Primary C-cell hyperplasia -> microinvasive MTC -> macroinvasive MTC
MEN IIA (Sipple Syndrome)

- Most common syndrome associated with MTC
- 3 distinct features
  - MTC
  - Pheochromocytoma
  - Parathyroid hyperplasia
- Involves multiple mutated codons on the RET proto-oncogene
  - 634 (most common)
    - Cutaneous amyloidosis
  - 609, 611, 618, 620
Familial Medullary Thyroid Carcinoma

- Stand alone or subset of MEN IIA?
- Diagnosis:
  - MTC in 2 or more generations without the presence of parathyroid hyperplasia or pheochromocytoma
  - Codons involved: 609, 618, 620, 804
    - Rarely ever see 634
MEN IIB

• Very rare
• Much more aggressive
• Features
  – MTC
  – Pheochromocytoma
  – Musculoskeletal manifestations
    • Marfanoid habitus
    • Pes cavus
    • Pectus excavatum
    • Proximal muscle weakness
  – Mucosal neuromas
  – Urinary and intestinal malformations
• Codon involved is 918

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RET Mutations – Who Should Be Screened?

- ATA Recommendations
  - Diagnosed with MTC
  - Features of MEN IIA/IIB or FMTC
  - C-cell hyperplasia
  - Family history of MEN IIA/IIB or FMTC (50% risk)
  - Patient with Lichen amyloidosis
    - Lesion in mid-upper back that is extremely pruritic that improves in sunlight
    - Associated with mutation in codon 634
  - Hirschsprung disease
    - Associated with mutation in exon 10 of RET
Prophylactic Thyroidectomy and RET Mutations

- Patients who are asymptomatic, but with known RET mutations should undergo prophylactic thyroidectomy

- Age at which this should occur depends on the mutation

- Mutations are grouped into 4 categories, A-D
  - D is the worst prognosis
  - A is the least likely to develop MTC
RET Mutation Categories

- **A**
  - Codons: 768, 790, 791, 804, 891
- **B**
  - Codons: 609, 611, 620, 630
- **C**
  - Codon: 634
- **D**
  - Codons: 918, 883
Prophylactic Thyroidectomy Based on Categories

- **D**
  - Thyroidectomy prior to 1 year of age
    - Pre-op U/S should be performed
    - Calcitonin not as reliable in this age group

- **C**
  - Thyroidectomy prior to 5 years of age
    - Pre-op U/S and calcitonin should be obtained at age 3

- **A,B**
  - May wait until after 5 years of age in 2 conditions
    - No aggressive family history of disease
    - Normal U/S and calcitonin levels
    - Pre-op U/S and calcitonin at age 3

- Any patient with a thyroid nodule >5mm or calcitonin >40 pg/mL should undergo total thyroidectomy
  - Higher risk of disease and metastasis
RET Mutation Identified, Any Other Tests?

- **Pheochromocytoma**
  - Screened by serum or 24-hour urine metanephrines/normetanephrines
  - Mutations involving codons 918 or 634
    - Screen for at age 10 and yearly after
  - All other mutations
    - Screen for at age 20 and yearly after

- **Hyperplastic Parathyroid Disease (MEN IIA)**
  - Screened by calcium and PTH
  - Mutations of 630 and 634
    - Screen for at age 8, and yearly after
  - All other mutations
    - Screen for at age 20, and yearly after
Older Patients Who Are Asymptomatic Carriers of RET Mutations

• What does older mean?
  – MEN IIA and FMTC – age > 5
  – MEN IIB – age > 1

• All should undergo U/S and calcitonin testing

• Calcitonin < 40 pg/mL and/or nodules < 5mm
  – Total thyroidectomy as soon as possible

• Calcitonin > 40 pg/mL and/or nodules > 5mm
  – Total thyroidectomy + central neck dissection

• If U/S showed nodes > 1cm in lateral neck
  – Perform neck dissection, levels IIa – V + thyroidectomy + central neck dissection

• Benefit of neck dissection with calcitonin < 40 pg/mL and/or thyroid nodules < 5mm has not proven beneficial
Management of Removed or Devascularized Parathyroid Glands

- RET mutations associated with MEN IIA (634, 620, 618, 609)
  - Place in forearm and mark
    - Reason:
      1. High risk of hyperplasia
      2. High risk of re-operation in the neck that could lead to injury of re-implanted parathyroid gland

- Other RET mutations
  - Recommended in forearm for same reason above, but highly unlikely to develop hyperplasia
Making the Diagnosis

- Two main tests
  - FNA
  - Serum calcitonin
    - Pentagastrin stimulated calcitonin is no longer available in the U.S. and rarely available in other countries

- FNA
  - Good at detecting disease, but disease detected later
  - Chang et al
    - Reviewed slides of 34 patients with known MTC
    - 82% were correctly diagnosed by FNA
    - 3 patients - follicular neoplasm
    - 1 patient – desmoid tumor (benign, but aggressive tumor seen in Gardner syndrome)
    - 2 patients – suspicious for MTC
    - Concluded:
      - All patient would have required surgery, and would have been correctly diagnosed with MTC

- Papaparaskova et al
  - 89% of cases reviewed had correct diagnosis by FNA alone
  - 99% of patients went for surgery where correct diagnosis was obtained
Making the Diagnosis

- **Serum Calcitonin**
  - Better at detecting earlier disease
  - **Controversy comes in cost analysis**
    - MTC represents 0.3-1.4% of all thyroid nodules
    - Should we screen everyone with thyroid nodules?

- **Elisei et al**
  - Examined 10,864 patient with thyroid nodules who were screened with serum calcitonin or FNA
  - 0.40% had MTC
  - Patients who had MTC detected by serum calcitonin prior to FNA
    - 59% remission rate after treatment
  - Patients who had MTC detected by FNA alone
    - 2.7% remission rate after treatment
What Serum Calcitonin Level is Indicative of MTC?

- **Costante et al**
  - Reported the PPV of serum calcitonin in the detection of MTC
    - 20-50 pg/mL – 8.3%
    - 51-100 pg/mL – 25%
    - > 100 pg/mL – 100%
MTC is Suspected, Now What?

- **Labs**
  - Serum calcitonin (if not already obtained)
  - Serum CEA
  - RET proto-oncogene mutation testing
    - If RET is positive
      - Screen for pheochromocytoma
      - Screen family members
  - Serum calcium
MTC is Suspected, Now What?

- **Imaging**
  - **U/S**
    - Assess the thyroid, level VI, lateral necks, superior mediastinum
  - **Nodes (+) and/or calcitonin > 400 pg/mL**
    - CT neck and thorax
    - Triple phase contrast enhanced CT of the liver or MRI of liver

- **Machens et al**
  - **Found:**
    - Distant metastasis present - calcitonin > 400 pg/mL and/or primary tumor > 1.2cm
    - Calcitonin 15,000 or primary tumor 5cm – 50% had metastatic disease
    - Calcitonin > 100,000 or primary tumor > 6cm – 100% had metastatic disease
Staging

- **TNM Staging**
  - T1 – Primary tumor ≤ 2cm
  - T2 - > 2cm – 4cm
  - T3 - > 4cm or minimal extrathyroidal extension (invasion of STRAP muscles)
  - T4a – Invasion of trachea, esophagus, larynx, recurrent laryngeal nerve
  - T4b – Tumor encases carotid or major mediastinal vessels or invading prevertebral fascia

  - N0 – no nodes
  - N1a – Level VI nodes only
  - N1b – Lateral neck nodes

  - M0 – no mets
  - M1 – distant mets

- **Important staging features**
  - N1a = Stage III
  - N1b = Stage IVa
  - T4a = Stage IVa
  - T4b = Stage IVb
  - M1 = Stage IVc
Surgical Treatment

• Pheochromocytoma present
  – Must be treated first

• Limited local disease (≤ T3)
  – No nodes detected
    • Total thyroidectomy + Level VI dissection
  – Level VI nodes detected
    • Total thyroidectomy + Level VI dissection
  – Lateral neck nodes detected
    • Total thyroidectomy + Level VI dissection + Level IIa-V neck dissection of side with nodes
**Surgical Treatment**

- **Advanced disease (T4a, T4b, M1)**
  - Palliative treatment since will not cure these patients
    - Medullary carcinoma at this stage is multifocal and involves multiple organ systems
  - Goal = preserve speech, swallow, and parathyroid function
  - Panel members of the American Thyroid Association split
    - Some recommended complete resection of disease (including laryngectomy, pharyngectomy, esophagectomy) followed by XRT
    - Others recommended debulking, tracheostomy (if needed), and clinical trials with or without hepatic embolization
  - Multiple studies have shown that when MTC is advanced, extent of surgery has no effect on survival
Recurrent Laryngeal Nerve

- Does the Nerve work?
  - Yes
    - Disease is confined to the neck, and cannot be removed from nerve
      - Take nerve
    - Disease extracervical or very advanced
      - Leave nerve
  - No
    - Take nerve
Post-operative Evaluation and Treatment

- **Post-op Calcitonin**
  - Important for tumor surveillance
  - Takes 1-2 months to normalize following surgery
    - Draw 2-3 months post-op
  - Undetectable
    - Observe these patients
    - 97% survival rate at 10 years
    - 3% risk of recurrence
  - Detectable
    - < 150 pg/mL
      - Less likely to find metastatic disease
      - Neck U/S advised
      - May consider CT scans, but unlikely to detect disease
    - > 150 pg/mL
      - Distant metastasis should be considered
      - Neck U/S, CT neck and thorax, triple phase liver CT, bone scan
Post-operative Evaluation and Treatment

• Calcitonin is detectable and disease is found

  – Calcitonin ≥ 150 pg/mL and nodes < 1cm
    • Observation

  – Calcitonin ≥ 150 pg/mL and nodes > 1cm
    • Surgical resection
      – If compartment has not been dissected previously – formal dissection
      – If dissection has occurred – remove gross disease

  – Distant metastasis (extracervical disease)
    • Palliative measures
Post-operative Evaluation and Treatment

- Calcitonin detectable and disease is NOT found
  - Observation only
  - Surgeons have attempted extensive neck dissections and mediastinal node removal without any improvement in survival
Post-operative Evaluation and Treatment

• Diagnostic Laparoscopy with examination of the liver
  – Used to be performed when calcitonin was detectable post-op and imaging was negative
  – No longer recommended by ATA
    • If this was (-) -> extensive neck dissections were performed
      – Does not improve survival
      – Increases morbidity
  • Imagining studies are much more sensitive than they used to be
Role of Calcitonin Doubling Time in Post-op Period

- Ct-DT – independent predictor of survival
  - < 6 months
    - 5 yr survival = 25%
    - 10 yr survival = 8%
  - 6-24 months
    - 5 yr survival = 92%
    - 10 yr survival = 37%
  - > 24 months
    - All patients were alive past 10 years
Role of External Beam Radiation

- Decreases relapse rate in some cases
- Does not improve survival
- Brierley et al
  - Used EBRT in patients with microscopic residual disease, local soft tissue invasion, and node positive disease
  - Local/regional relapse rate = 86%
    - 52% in those who did not receive EBRT
- Chow et al
  - Used EBRT in patients with nodal positive disease
  - 4/4 patients who received EBRT had locoregional control
  - 1/3 patient who did not receive EBRT had locoregional control
ATA Recommendations for EBRT

- Microscopic disease present ( + margins)
- Node (+) disease with detectable calcitonin

- If there were no nodes, margins (-), and calcitonin is detectable
  - ATA does NOT recommend EBRT
    - Unknown location of disease
Chemotherapy

- MTC does not respond well to chemotherapeutic agents

- Partial, but short-lived remission has been seen in 10-20% of cases
  - Dacarbazine, 5-FU, and doxorubicin

- ATA does not recommend chemotherapy in the treatment of MTC
Future Therapies

- Focusing on radioimmunotherapy and vaccine-based therapies

- Compounds that block kinase function
  - Shown to decrease MTC cell proliferation

- Vascular endothelial growth factor and its receptors are another target
Conclusion

- Rare, but potentially deadly form of thyroid cancer
- Early detection and treatment is paramount in patient survival
- RET mutations must be identified, and family members screened
- Surgery is the primary treatment with the aim of removing all possible disease
- EBRT has shown some improvement in relapse rate, but not survival
  - Cannot be relied upon