Cowden Syndrome & Thyroid Cancer

Pediatric Grand Rounds, 12/18/15
Dawn McDaniel, MD – PGY3

Case 1

- CC: Intermittent back pain
- HPI: A 5/10 yo male who presents for re-evaluation by his Endocrinologist since his most recent ultrasound continued to show a thyroid nodule.
- He was lost to follow-up with his medical providers as a result of “family illness.”
- MOC notes enlargement of the lipomas on his back which cause him pain on occasion. He is otherwise well. No known trauma.
- ROS:
  - Endorses: abnormal curvature of chest, lumps on his back, thyroid nodule on recent ultrasound
  - Denies: fatigue, tachycardia, dry skin, constipation, sweating, headaches, poor appetite, diarrhea, weight loss, weight gain.

History Cont’d

- PMH:
  - Asthma
  - Anxiety
- PSH: none
- FFS:
  - Cowden Syndrome on MOC’s side of family
  - MOC: thyroid cancer, LUE AVM
  - MGM: goiter, skin findings
  - Brother: thyroid cancer +/p thyroidectomy
  - MGM: HTN and HUP
  - M-uncle - testicular cancer
  - All: NKDA
- Meds: none currently (h/o fluoxetine, Qvar, Pulmicort)

Physical Exam

- 12/18/2009 Brain MRI - normal intracranial evaluation
- 5/21/2010 Spine films - minimal 4 degree, dextro curvature of T1 spine (T7-L1)
- 10/02/2012 Soft Tissue U/S Neck - non-specific 2.6mm complex nodule deep within the right lobe of the thyroid
- 4/17/2014 Thyroid U/S - 262 mm hypoechoic nodule in R lobe of thyroid. 1X1 mm hypoechoic nodule in L lobe of thyroid. No increased vascularity.
- 5/28/2014 MRI Chest & Abdomen (x2) – Multi body wall lipomas, some are increased in size. Unchanged and severe pectus excavatum.
- 5/7/2015 Thyroid U/S - Unchanged 2 mm R thyroid lobe nodule. Previously noted 1 mm nodule in the L thyroid lobe is not identified on today’s study.

Rads

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Financial Disclosure

- No relevant financial interests.
Case 2

- CC: Weight gain
- HPI: 13-10/12 yo male with h/o papillary thyroid cancer s/p total thyroidectomy with multiple complications and subsequent radio-ablation. Presents for follow-up with his Endocrinologist.
- Since his last visit, he has been more compliant with taking his Levothyroxine dose, mostly a result of frequent reminders by MOC. MOC attributes his weight gain to increased fast food (mostly fries) and drinking sodas. He is always hungry. His weight gain has caused stretch marks on his abdomen, but he has not had to change clothing sizes.
- He is on a replacement (T4) dose of 150 mcg daily and TSH from last visit showed significantly elevated TSH (28.6) and normal T4.

- ROS:
  - Endorses: weight gain, exercise intolerance, intermittent constipation
  - Denies: fatigue, tachycardia, dry skin, sweating, headaches, poor appetite, diarrhea, weight loss

History Cont’d

- PMH:
  - Celiac disease
  - Exercise-induced rhinitis
  - Papillary thyroid carcinoma
  - Bilateral vocal cords paralyzed (post op)
  - Acquired hypothyroidism
  - Acquired hypoparathyroidism (resolved)
  - Medications:
    - Levothyroxine
    - Calcium supplements
  - Allergies:
    - Media, Levothyroxine 150 mcg daily, Ergocalciferol 50K units q4wks (Previously on Calcium supplements)
  - Social:
    - Lives with parents, brother Developmentally normal

Physical Exam

- Neck:
  - No tracheal deviation
  - Thyromegaly
  - Thyroid gland: bilateral, normal, no palpable lumps, no palpable lymph nodes
  - Thyroid isthmus: normal
  - Nondiscrete, firm, nodular masses

- Head:
  - no exophthalmos
  - Temporal arteries: normal
  - No nontender lymph nodes

- Pharynx:
  - No tonsilar exudate
  - No cervical adenopathy

- General:
  - Normocephalic
  - No palpable masses
  - No nontender lymph nodes

Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Value 1</th>
<th>Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid stimulating hormone</td>
<td>2.44 (2)</td>
<td>3.85 (3)</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.6 (4)</td>
<td>9.5 (5)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>67 (6)</td>
<td>8.6 (7)</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>26.6 (8)</td>
<td>15.8 (9)</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.6 (10)</td>
<td>9.5 (11)</td>
</tr>
<tr>
<td>Parathyroid hormone activity</td>
<td>10 (12)</td>
<td>10 (13)</td>
</tr>
</tbody>
</table>

Pathology

- 8/14/12 Soft Tissue Head and Neck: No enlargement of thyroid lobes. B/l hypoechogenic nodules, most of them hyperemic. No calcifications.
- 9/18/12 US with FNA of nodules
- 12/18/2015 Spin films - minimal dextrosclerosis of TL spine with Cobb angle approx 9 degrees
- 8/22/14 NM Scan to f/u radioablation
Learning Objectives

- Be able to answer the following questions:
  - What is Cowden’s Syndrome?
  - What are the genes involved and their typical function?
  - What are other syndromes associated with this gene?
  - How is CS diagnosed?
  - What cancers are associated with CS and their lifetime risks?
  - What are the different types of thyroid cancers and their relative importance in the pediatric patient population?
  - Which thyroid cancers are associated with CS?
  - What is recommended screening for CS patients?

**Cowden Syndrome**

- A multiple hamartoma syndrome
  - A hamartoma is a non-cancerous, abnormal tumor-like growth made up of the same tissue from which it grows
  - Result of mutation in PTEN gene (300+ different gene mutations; other genes commonly involved)
- Autosomal dominant inheritance for germline mutations
- High risk for benign & malignant tumors
  - Thyroid: lifetime risk 46%
  - Breast: lifetime risk 85%
  - Endometrium: lifetime risk 28%
  - Colon: lifetime risk 8%
  - Kidney: lifetime risk 9%
  - Melanoma: lifetime risk 6%

**CS vs. General Population Risk**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>General Population Risk</th>
<th>Cowden Syndrome Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>3.8%</td>
<td>24%</td>
</tr>
<tr>
<td>Breast</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1.9%</td>
<td>28%</td>
</tr>
<tr>
<td>Colon</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Kidney</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0.05%</td>
<td>6%</td>
</tr>
</tbody>
</table>

**What is PTEN?**

- Phosphatase and Tensin Homolog (AKA: MMAC1 & TEP1)
- A phosphatase enzyme functions as a tumor suppressor
- Part of family of genes PTP (protein tyrosine phosphatases)
- Located 10q23.3 (Base pair 87,863,437 to 87,917,929)
- Mutation (a few base pairs to large deletions) → poor or absent function of enzyme
- Somatic mutations in PTEN among the most common genetic changes found in human cancers (#1 prostate cancer, endometrial cancer; Commonly: glioblastomas, astrocytomas, melanoma)

**PTEN Cont’d**

- Signals cells to stop dividing and triggers apoptosis
- Evidence suggests helps control cell migration, adhesion to surrounding tissues, and angiogenesis
- Likely plays a role in maintaining stability of DNA
Other PTEN mutation syndromes

- **Bannayan-Riley-Ruvalcaba syndrome**
  - Congenital d/o, intestinal hamartomous polyposis, lipomas, pigmented macules of glans penis
  - Many similarities with CS. May be a spectrum disorder.
- **PTEN-related Proteus syndrome** (Segmental overgrowth, lipomatosis, arteriovenous malformations, and epidermal nevus (SOLAMEN) syndrome; Type 2 segmental Cowden syndrome)
  - Congenital malformations and hamartomous, asymmetric overgrowth of multiple tissues (bones, skin, and other tissues), connective tissue nevi, epidermal nevi, and hyperostoses
- **Proteus-like syndrome**
  - Significant clinical features of PS not meeting all criteria

Clinical Diagnostic Criteria

- **Major Criteria:**
  - Breast cancer
  - Endometrial cancer
  - Follicular thyroid cancer
  - Multiple GI hamartomas or ganglioneuromas
  - Macrocephaly
  - Macular pigmentation of glans penis
  - Muco-cutaneous lesions
    - One biopsy proven trichilemmoma
    - Multiple palmpoplantar keratosis
    - Multifocal or extensive oral mucosal papillomatosis
    - Multiple cutaneous facial papules (often verrucous)

- **Minor criteria:**
  - Autism spectrum disorder (BRRS)
  - Colon cancer
  - 3 or more esophageal glycogenic acanthoses
  - Lipomas
  - Intellectual disability (IQ<75)
  - Papillary or follicular variant of papillary thyroid cancer
  - Thyroid structural lesions (adenoma, nodule, goiter)
  - Renal cell carcinoma
  - Single GI hamartoma or ganglioneuroma
  - Testicular lipomatosis
  - Vascular anomalies (incl mult intracranial developmental venous anomalies)

Images

- *Images from VisualDx*

Clinical Diagnosis Cont’d

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The Diagnosis

- Confirmed diagnosis: Clinical criteria + genetic confirmation
- Presumed diagnosis: Clinical criteria – genetic confirmation
- Typically not diagnosed until adulthood (90% have some clinical manifestation by late 20s) unless family history present
- Criteria divided into Major and Minor
- Complex schema to meet clinical diagnostic criteria
- If all criteria not met, can give diagnosis of Cowden-like syndrome.
Testing

- Pathology
  - Confirm histopathology of characteristic lesions

- Genetic Testing
  - PTEN pathogenic variant is identified on gene testing
    - Cowden Syndrome
      - 85% have a detectable PTEN pathogenic variant (as low as 25% in one study)
    - Bannayan–Riley–Ruvalcaba syndrome
      - 65% have a detectable PTEN pathogenic variant
    - Proteus-like syndrome
      - 50% have identifiable PTEN pathogenic variant
    - Proteus syndrome
      - 20% have identifiable PTEN pathogenic variant

Diagnostic Resources

- PHMO Genetic Team
  - Gail Tomlinson, MD, PhD, Medical Director
  - Lindsey Mette, MS, MPH, CGC, Genetic Counselor
  - Natalie Poullard, MS, CGC, Genetic Counselor

- Risk Calculator
  - Estimates a patient's risk for PTEN mutation
  - Cleveland Clinic's Lerner Research Institute
  - www.lerner.ccf.org

Thyroid Basics

- Thyroid is composed of follicles (colloid filled sacs)
- Thyroid is composed of different cell types:
  - Follicular - principal epithelial cell type → thyroid hormones
  - Parafollicular (C cells) - produce calcitonin (opposes action of PTH)

Thyroid Cancer

- Relevance
  - Most common endocrine malignancy in pediatrics
  - Children typically present with advanced disease (compared to adults). Nodules in children are more likely to be malignant than in adults (25–35%)
  - Increase incidence in pediatric thyroid cancers [6]
    - 2009 Study reviewed Surveillance, Epidemiology, and End Results (SEER) registry from 1973 through 2004
      - All patients with thyroid cancer who were younger than 20 years of age.
      - Annual incidence of thyroid cancer in this cohort has been increasing 1.1% per year
    - Plus data from UTHSCSA Pedi Endo
    - 1st-ever Guidelines published by the American Thyroid Association in April 2015 for evaluation and management of Pediatric Thyroid Nodules and Differentiated Thyroid Cancers
**Thyroid Cancer**

- Cancer types
  - Papillary Thyroid Carcinoma
  - Medullary Thyroid Cancer
  - Follicular Thyroid Cancer
  - Anaplastic Thyroid Cancer

**Major criteria in CS**
- Papillary Thyroid Cancer
- Medullary Thyroid Cancer
- Follicular Thyroid Cancer
- Anaplastic Thyroid Cancer

**Papillary Thyroid Cancer**

- Most common thyroid cancer
- Highly curable especially if caught early
- Associated with radiation exposure (particularly as therapy to treat children with different primary cancers)
- Usually have cold nodule on radioactive iodine scan
- Typical presenting symptom: palpable nodule in thyroid (painless with completely asymptomatic child)

**Papillary Thyroid Carcinoma Staging**

- Regional lymph nodes are the central compartment, lateral compartment, and upper mediastinal lymph nodes.

**Regional lymph nodes (N)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Regional lymph nodes</th>
<th>R0</th>
<th>R1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Regional nodes cannot be assessed</td>
<td>No regional lymph nodes</td>
<td>No regional lymph nodes</td>
</tr>
<tr>
<td>N1</td>
<td>Regional nodes are present</td>
<td>No regional lymph nodes</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis to level V (pretracheal, paratracheal, and paraesophageal)</td>
<td>Regional lymph nodes</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis to level VI (supraclavicular, prelaryngeal/Delphian)</td>
<td>Regional lymph nodes</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis to level VII (infraclavicular, jugular, or internal mammary)</td>
<td>Regional lymph nodes</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>N4</td>
<td>Metastasis to any other lymph node or non-lymphatic site</td>
<td>Regional lymph nodes</td>
<td>Regional lymph nodes</td>
</tr>
</tbody>
</table>

**Papillary Thyroid Carcinoma Prognosis**

- Anaplastic (typically found at stage 4)
  - 7% 5 yr survival
  - 65% 10 yr survival
- Medullary
  - 86% 5 yr survival
- Follicular
  - Similar to papillary
- ***Depends heavily on stage at time of diagnosis***

**Papillary Histologic Variants**

- Fibrovascular core

**Papillary Thyroid Histologic Variants**

- A: Typical
- B: Follicular
- C: Tall cell
- D: Columnar
Management and Treatment

- **Management and Treatment Cont’d**
  - **Surgical Resection of thyroid and adjacent lymph nodes**
    - Lobectomy, isthmectomy, total thyroidectomy
      - Who gets total:
        - Nodular goiter
        - Known distant mets
        - Extradural extension
        - Carcinoma
      - Cervical LN mets
      - Poorly differentiated histology
    - Recurrence risk: 5% at 20 yrs for total vs 22% at 20 yrs for lobectomy [4]
    - In CS specifically, recurrence risk increases with younger age at diagnosis
    - Complications:
      - Hypothyroidism
      - Orophagia
      - Venous cord paralysis
      - Hypoparathyroidism
  - **Radioactive Iodine Ablation**
    - 4-6 wks after surgery (destroy mets vs residual tissue)
    - Stop thyroid supplementation prior to induce hypothyroid state and promote high TSH
    - Diagnostic dose 131I or 123I followed by therapeutic dose to ablate tissue
    - Complications: [5]
      - Radiation thyroiditis and transient thyrotoxicosis
      - Sialadenitis
      - Nausea, anorexia, PA
      - Pulm fibrosis if large lung mets
      - Brain edema if brain mets (less with glucocorticoid therapy)
    - Complications: [6]
      - Increased risk of leukemias, breast, and bladder carcinoma
    - Complications: [7]
      - Transient menopausal irregularities and early menopause
      - Teratogenesis/spontaneous abortions
      - Experts suggest women wait up to 1 year before attempting pregnancy
    - **Surveillance in CS**
      - **Goal:** To detect tumors at the earliest, most treatable stages.
      - **Children:** Yearly thyroid U/S and skin check with PE
      - **Adults:** Yearly thyroid U/S and dermatologic evaluation
        - Women beginning at age 30 yrs: qmo breast self-exam; annual breast screening (mammo at minimum; consider MRI) and transvaginal U/S or endometrial biopsy
        - Men and women: colonoscopy beginning at age 35 years with frequency dependent on degree of polyposis identified; biannual (every 2 yrs) renal imaging (CT or MRI preferred) beginning at age 40 yrs.
      - Those with FHx of a particular cancer at an early age: consider initiating screening 5-10 years prior to youngest age of diagnosis in the family.
  - **Screening Recs from ACG**
    - **Colon Cancer Risk**
      - [1]"
Screening Recs from ACG

<table>
<thead>
<tr>
<th>Site</th>
<th>Age to begin Surveillance</th>
<th>Surveillance procedures and comments</th>
</tr>
</thead>
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Summary
- Cowden’s Syndrome is a multiple hamartomatous disease that is a result of dysfunction of the PTEN tumor suppressor gene.
- This disorder conveys increased risk for different types of cancers.
- CS is diagnosed clinically with genetic confirmation.
- There are four broad categories of thyroid cancer which has a rising incidence in recent years.
- Screening for multiple types of cancers in patient with CS is recommended but the weight behind these recommendations is weak.

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Appreciation
- Thanks to:
  - Dr. Shafqat Shah
  - Dr. Melissa Frei-Jones
  - Lindsey Mette
  - Dr. Carisse Orsi
  - Dr. Gail Tomlinson

References