60 year old male with rising calcitonin levels

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Fellow Adult Endocrinology
No disclosures
Objectives

- To discuss the role of calcitonin in follow up of patients with medullary thyroid cancer
- To define the roles of imaging studies for patients with increased calcitonin levels
Case Presentation

60 year old male with medullary thyroid cancer

- Referred by Endocrine surgery to Endocrinology here for a rising calcitonin level
- Background
  - Found to have a neck lump in 2009, FNA at OSH
  - Underwent right thyroidectomy OSH in 2009, once diagnosed with MTC referred to Endocrine Surgery here
Pre-op Evaluation for Medullary Thyroid Cancer

Labs

- plasma metanephrines: Normetanephrine 59, Metanephrine 20
- serum calcium, PTH: 9.4
- Calcitonin, CEA: 176, 4.4
- RET germline mutation: A mutation was NOT detected

Imaging

- CT Neck Chest, Abdomen, Pelvis: Enlarged Para tracheal, anterior mediastinal LNs
ROS

- Constitutional: **Positive for fatigue. Unexpected weight change (lost 20lbs in 8 months)** Negative for chills and fever.

- HENT: some hoarseness, and he has to clear his throat frequently

- Respiratory: Negative for shortness of breath and stridor. **Positive for cough and shortness of breath**

- Cardiovascular: Negative for chest pain.

- Gastrointestinal: Negative for abdominal pain and vomiting, **trouble swallowing (with pills only), diminished appetite**

- Neurological: Negative for tremors and syncope.

- Genitourinary: Positive for urgency.

- Musculoskeletal: **Positive for knee pain and back pain.**

- Psychiatric/Behavioral: Negative for confusion. **Positive for decreased concentration (forgetfulness). The patient is nervous/anxious (he notes occasional panic attacks).**

- All other systems reviewed and are negative.
Background

- May 2011: completion left thyroidectomy, lateral LN dissection (II, III, IV, V) with auto parathyroid transplantation
- Follows up with OSH Endocrinology, Calcitonin 131 > 150
- Imaging CT neck, chest: no evidence of any overt neck masses
- ‘…radiographic imaging and clinical evaluation does not point to any source for the calcitonin levels…’
### Background

- Oct 2014: Repeat CT Neck, Chest was ordered and referred to Endocrine surgery

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<tbody>
<tr>
<td>Calcitonin ((&lt; 16))</td>
<td>176&gt;130</td>
<td>150</td>
<td>255</td>
<td>353</td>
<td>333</td>
<td>446</td>
<td>469</td>
<td>563</td>
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<tr>
<td>CEA (0-3.4)</td>
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<td>18.7</td>
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Background Pathology

No tumor left thyroid lobe...

Immunostains for calcitonin, synaptophysin, chromogranin and CEA strongly positive in lymph nodes.
Background Imaging

- Feb 2014 PET CT scan: Without convincing abnormal FDG activity to suggest metastatic disease
- Oct 2014: Repeat CT Neck, Chest: Small pre vascular and right upper mediastinal LNs 9x14mm (previously 7x11mm in 2011)
- Referred to Endocrine surgery
- Nov 2014 Octreotide Scan: No evidence of disease
- Dec 2014 MRI Liver: No evidence of disease
- Referred to Endocrinology here
Background Case Treatment: Surgery

Dec 10 2014:

Left neck dissection negative

Lymph node metastases 11/13, largest 1.4 cm
**Other PMH/PSH:**
- BPH
- DVT
- HTN
- Post surgical hypothyroidism
- Pulmonary embolus
- Renal cell cancer (s/p laparoscopic left partial nephrectomy 2012)
- Rheumatoid arthritis
- Partial right parotidectomy for lipoma

**Allergies:**
IV contrast – Hives

**Medications:**
- alprazolam 1 mg bid prn
- apixaban 5 mg bid
- diltiazem 240 mg daily
- fenofibrate 160 mg daily
- finasteride 5 mg daily
- fluticasone 2 Sprays prn
- hydroxychloroquine 200 mg daily
- leflunomide 20 mg daily
- levothyroxine 125 mcg daily
- lisinopril 40 mg daily
- omeprazole 20 mg
- trazodone 150 mg every night

**Family history:**
- CAD Father/Brother
- Breast cancer Sister
- Papillary Thyroid Cancer Sister
- HTN Sister

**Social history:**
- Former smoker 1 ppd for 5 years, quit > 30yrs ago, no alcohol, no illicit drugs
- Not currently working
Physical Exam

Constitutional: He is oriented to person, place, and time. He appears well-developed and well-nourished. No distress.

HENT: NCAT, EOMI, PERRL


Cardiovascular: Normal rate, S1 + S2 no M/R/G

Pulmonary/Chest: CTAB no wheeze/rales/rhonchi

Neurological: A&O x 3. No cranial nerve deficit.

Skin: Skin is warm and dry. No erythema.

Psychiatric: normal mood and affect.
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<tbody>
<tr>
<td>Calcitonin</td>
<td>563</td>
<td>387</td>
<td>316</td>
<td>429</td>
<td>549</td>
<td>416</td>
<td>854</td>
<td>759</td>
<td>906</td>
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<tr>
<td>CEA</td>
<td>18.7</td>
<td>11.9</td>
<td>12.6</td>
<td>12.4</td>
<td>12.4</td>
<td>14.6</td>
<td>16.2</td>
<td>16.4</td>
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How would you suggest to localize the lesion?
What is the Dotatate Scan?

Dotatate aka 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid(DOTA).-Tyr3octreotate

NET have Somatostatin receptors expressing tumors

Bind to peptides, Rp mediated internalized and intracellular retention

This can be exploited in imaging by chelating with positron-emitting radionuclides, usually gallium-68-Dotatate (Peptide receptor imaging)

This permits imaging in a PET camera which has better sensitivity and higher resolution than the gamma camera, which results in better image quality.

The most commonly used tracers or radiopeptides 68Ga-DOTATOC, 68Ga- DOTATATE and 68Ga-DOTANOC

Couple with radioactive isotopes use for PRRT (peptide receptor radio therapy) for tumor shrinkage by delivering high dose radiation to intracellular components of cancer. Effect not seen with cold somatostatin analogues.
Imaging

- Numerous studies have demonstrated superior accuracy of 68Ga-DOTATATE/DOTATOC compared with either conventional radiologic imaging or 111In-octreotide scintigraphy for evaluation of NET, with a pooled sensitivity of 93% and specificity of 96% in a recent large meta-analysis.

- Technetium-99m-DMSA-V was mainly used in the detection of MTC but the sensitivity was counterbalanced by instability of the component and low specificity with non-tumoral uptake such as in areas of inflammation, bone fractures and other types of tumors. It is now unavailable commercially.

- Indium-111-octreotide sensitivity ranging from 37% to 75%.

- 123I-MIBG SPET/CT, which detects uptake in intra-cellular granules. 18F-FDG PET/CT which detects increased metabolic activity and utilization of glucose by tumor cells. Recurrences are only detected in 40% of cases.

- Improved resolution of PET compared to SPET imaging with 123I-MIBG or 111I-octreotide.

- Gallium-68-Dotatate has also been shown to detect bone metastases that were not suspected clinically or radiologically.
## Clinical Indications for the Dotatate Scan

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<th>Category</th>
<th>Indication</th>
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<td><strong>Staging</strong></td>
<td>Prior to resection of apparently localized disease</td>
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<td><strong>Localization</strong></td>
<td>Primary site in patients with biochemical suspicion of NET</td>
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<td>Unknown primary with metastatic NET</td>
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<td><strong>Theranostic (therapy and diagnostics)</strong></td>
<td>SSTR density &amp; distribution to guide suitability for SSA therapy or PRRT</td>
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<td><strong>Therapeutic</strong></td>
<td>Restaging response assessment</td>
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<td>Suspected disease recurrence post-surgery (e.g. rising tumor markers)</td>
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May 2017:
Increased tracer activity within the superior mediastinum and a pre vascular lymph node consistent with metastatic medullary thyroid carcinoma
Follow up

• Jan 2018 CT Neck: Evidence for progression of disease

What do we do now?
Patient treatment options:

- Continued observation and follow up
- Oncology: Role of TKI (2 FDA approved drugs: cabozantinib and vandetanib)
- Role of external beam radiation
- Therapeutic application of Beta -emitting Yttrium-90 and Lutetium-177 for PRRT (peptide receptor radionuclide therapy), individualize treatment depending on extent of disease
- LUTATHERA® (lutetium Lu 177 dotatate) FDA approved for Gastro-pancreatic Neuroendocrine tumors Jan 2018)
Take Home points

• Dotatate scan is available here for management of NET

• New targeted therapies are becoming available (Peptide receptor radionuclide therapy for treatment of NET)
Acknowledgements

- Dr Cohen
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