Dr. Darji does not have any relevant financial relationships with any commercial interests.
ENDORAMA:
60 Year Old Woman On Immune Checkpoint Inhibitor With Hyperthyroidism

Monika Darji
October 25th, 2018
Objectives

• Review the endocrine related adverse effects associated with immune checkpoint inhibitors
• Discuss the range of thyroid dysfunction induced by immune checkpoint inhibitors
• Discuss the management of thyroid disorders associated with immune checkpoint inhibitors
Chief Complaint

60 year old Caucasian female presents with weight loss, tremors, and diarrhea
HPI

• Patient reports the following symptoms over the last 6 weeks:
  • 15 lb unintentional weight loss
  • Multiple episodes of diarrhea daily
  • Tremor involving both hands and arms
  • Heat intolerance
  • Palpitations
  • Muscle weakness

• Patient was directly admitted from Oncology clinic
Oncology History

• Patient was diagnosed with metastatic melanoma in 6/2018
  • pT3N1, stage IIIc disease per AJCC 8th ed
  • Lesion on the right side of neck s/p wide local excision
  • Irregular 3x2x2cm right parotid gland mass s/p parotidectomy, pathology positive for metastatic disease
  • Positive right cervical lymph node
  • Started adjuvant nivolumab in 7/2018 (received 3 doses)
Additional history

• ROS: Denies diaphoresis, anxiety. Denies neck masses or pain, voice changes, dysphagia, eye symptoms
• Past Medical History: type 2 diabetes, asthma
• Past Surgical History: neck lesion wide local excision, parotidectomy
• Family History: no family history of thyroid disease, father – colon cancer
• Social History: married with 3 kids, works in a factory, 45 pack year smoking history – quit in 2012. Denies alcohol and illicit drugs
Additional history

• Meds: metformin, albuterol prn, zofran prn

• Allergies: NKDA
Physical Exam

- Vitals: 74 kg, BMI 26, Temp 98.6, HR 110, RR 17, BP 132/84, SpO2 100%
- Constitutional: no acute distress
- HEENT: EOMI, no exophthalmos, no lid lag
- Neck: supple, diffuse thyromegaly, no thyroid nodules
- Cardiovascular: tachycardic, regular rhythm
- Pulmonary/Chest: good respiratory effort, clear to auscultation bilaterally
- Abdomen: soft, non-tender, nondistended
- Extremities: no edema
- Neurological: alert, oriented, 4/5 muscle strength in all four extremities, tremor in bilateral upper extremities
- Skin: warm, dry
- Psychiatric: not agitated
Admission Labs

Anion gap 13

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>0.01</td>
<td>0.3-4.0</td>
</tr>
<tr>
<td>Free T4</td>
<td>3.28</td>
<td>0.9-1.7</td>
</tr>
<tr>
<td>Total triiodothyronine</td>
<td>362</td>
<td>80-195</td>
</tr>
<tr>
<td>TSI negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Additional testing

- Patient had labs from 9/2018 completed in Oncology clinic
  
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.01</td>
<td>0.3-4.0</td>
</tr>
<tr>
<td>Free T4</td>
<td>2.31</td>
<td>0.9-1.7</td>
</tr>
</tbody>
</table>

- Thyroid ultrasound showed increased vascularity and no discrete nodules
Immune Checkpoint Inhibitors (ICI)

- Monoclonal antibodies that block immune inhibitory ligands CTLA-4 and PD-1
- First agent approved in 2011
- Have significantly improved the life expectancy of patients with certain malignancies
  - Used in melanoma, lung cancer, renal cell carcinoma
- Additional drugs in development
How does it work?

- ICIs work by reversing the mechanisms that normally block immune responses to malignancy and in maintaining control of antitumor immunity
- ICIs block negative regulators (checkpoints) of T-cell activation and function
CTLA-4

• Present in lymph tissue
• CTLA-4 present in naïve T-cells and regulatory T-cells
• Binds to CD 80/86 on antigen presenting cells to inhibit immune response
• CTLA-4 inhibitors = ipilimumab and tremelimumab
PD-1 and PD-L1

• Present in peripheral tissues, PD-1 expressed on chronically activated T-cells. PD-L1 expressed on stromal cells, tumor cells, and antigen-presenting cells
• Binding -> inhibits immune response
• PD-1 inhibitors = nivolumab and pembrolizumab
• PD-L1 inhibitors = atezolizumab, avelumab, and durvalumab
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Name</th>
<th>Melanoma</th>
<th>NSCLC</th>
<th>RCC</th>
<th>HL</th>
<th>Urothelial</th>
<th>HNSCC</th>
<th>Merkel</th>
<th>MSI-H</th>
<th>CRG</th>
<th>Gastric</th>
<th>HCC</th>
<th>MSI-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA4 blockade</td>
<td>Ipilimumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremelimumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD1 blockade</td>
<td>Nivolumab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDL1 blockade</td>
<td>Atezolizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avelumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CTLA4 = cytotoxic T-lymphocyte antigen 4; FDA = US Food and Drug Administration; HCC = hepatocellular carcinoma; HL = Hodgkin lymphoma; HNSCC = head and neck squamous cell carcinoma; MSI-H = microsatellite instability-high cancer, unresectable or metastatic; MSI-H CRC = microsatellite instability-high colorectal cancer NSCLC = non-small cell lung cancer; PD1 = programmed death 1; PDL1 = programmed death 1 ligand; RCC = renal cell carcinoma.*
Immune related adverse events (irAE)

• Typical irAEs affect skin, GI tract, liver, and endocrine system
• Rare irAEs include uveitis, conjunctivitis, neuropathy, myopathy, pancreatitis, pneumonitis, cytopenias, and nephritis
• Endocrine irAEs often irreversible
  • Autoimmune thyroid disease, hypophysitis, adrenal insufficiency, type 1 diabetes
Endocrine irAEs

- Pituitary gland
  - Hypophysitis
  - Corticotropin (ACTH) decrease
  - Secondary adrenal insufficiency

- Thyroid gland
  - Hyperthyroidism
  - Hypothyroidism
  - TSH increase or decrease
  - Thyroiditis
  - Free thyroxine increase or decrease
  - Autoimmune thyroiditis

- Adrenal glands
  - Primary adrenal insufficiency

- Pancreas
  - Diabetes mellitus
Incidence

• Barroso-Sousa et al. published a systematic review and meta-analysis that included 7551 patients in 38 randomized trials in JAMA Oncology 2018
• The overall incidence of endocrinopathies is approximately 10% of patients treated with ICIs
• Endocrine irAEs were significantly higher with combination therapy compared with monotherapy
• Among patients on monotherapy regimens
  • Incidence of thyroid dysfunction was higher in those treated with anti–PD-1 agents
  • Incidence of hypophysitis was highest in those treated with ipilimumab
• No association between the tumor type and the incidence of ICI-induced thyroid dysfunctions
Incidence

- The overall incidence of hypothyroidism estimated to be 6.6% (95% CI, 5.5%-7.8%)
- The overall incidence of hyperthyroidism estimated to be 2.9% (95% CI, 2.4%-3.7%)

* Combination = nivolumab plus ipilimumab
Incidence

The overall observed incidence of hypophysitis

- 6.4% with combination therapy
- 3.2% with CTLA-4 inhibitors
- 0.4% with PD-1 inhibitors
- <0.1% with PD-L1 inhibitors

*eTable 3. Meta-regression model results for any grade hypophysitis in patients with melanoma*

<table>
<thead>
<tr>
<th>Class</th>
<th>Predicted Incidence, % (95% PI)</th>
<th>Odds ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICI regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTLA-4</td>
<td>3.8 (2.7 - 5.2)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>PD-1</td>
<td>1.1 (0.8 - 1.6)</td>
<td>0.29 (0.18 - 0.49)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Combination</td>
<td><strong>8.0 (5.9 - 10.8)</strong></td>
<td>2.24 (1.39 - 3.60)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

* Combination = nivolumab plus ipilimumab
Onset of endocrine irAEs

• For ipilimumab, the median time to onset of endocrine irAEs ranged from 7–20 weeks
  • Hypophysitis - Median time to onset of symptoms was 4 months
  • Hypothyroidism - Median time to onset of symptoms was 5 months
• For nivolumab, median time to onset of symptoms was:
  • Hypophysitis - 4.9 months (range: 1.4–11 months)
  • Adrenal insufficiency - 4.3 months (range: 15 days to 21 months)
  • Hypothyroidism or thyroiditis resulting in hypothyroidism - 2.9 months (range: 1 day to 16.6 months)
  • Hyperthyroidism - 1.5 months (range: 1 day to 14.2 months)
• For CTLA-4 inhibitors, studies have shown worsened toxicity with higher doses
• For PD-1 inhibitors, overall toxicity is similar across a wide dose range
Monitoring

• Baseline TSH and free T4 level should be checked before beginning treatment with ICI
  • Should be monitored at least monthly for the first six months
  • If no abnormalities during the first six months and the patient is asymptomatic, TSH and free T4 can be checked quarterly for months 6 to 12 and then every six months
Thyroid dysfunction

Table 2. Possible immunotherapy-induced changes in thyroid function based on laboratory values

<table>
<thead>
<tr>
<th>TSH</th>
<th>Free T4</th>
<th>T3 total</th>
<th>Possible diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Normal-high</td>
<td>Normal-high</td>
<td>Transient thyrotoxic phase of thyroiditis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Graves’ disease (less common)</td>
</tr>
<tr>
<td>Low or normal</td>
<td>Low</td>
<td>Low</td>
<td>Secondary hypothyroidism due to hypophysitis/pituitary dysfunction†</td>
</tr>
<tr>
<td>High</td>
<td>Low-normal</td>
<td>Low-normal</td>
<td>Primary hypothyroidism/hypothyroid phase of thyroiditis*</td>
</tr>
</tbody>
</table>

*May evolve from a thyrotoxic phase to permanent hypothyroidism. TSH = thyroid-stimulating hormone.
†Thyroid hormone therapy should be instituted together with adrenal steroid replacement, unless adrenal insufficiency has been ruled out.

Hypothyroidism is the most common thyroid abnormality
# Hypothyroidism

<table>
<thead>
<tr>
<th>Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1: TSH &lt;10 mIU/L and asymptomatic.</td>
<td>- Should continue ICPI with close follow-up and monitoring of TSH, FT4.</td>
</tr>
</tbody>
</table>
| G2: Moderate symptoms; able to perform ADL; TSH persistently >10 mIU/L. | - May hold ICPI until symptoms resolve to baseline.  
- Consider endocrine consultation.  
- Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist >10 mIU/L (measured four weeks apart).  
- Monitor TSH every six to eight weeks while titrating hormone replacement to normal TSH.  
- FT4 can be used in the short term (two weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low.  
- Once adequately treated, should monitor thyroid function (at least TSH) every six weeks while on active ICPI therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable. |
| G3 to 4: Severe symptoms; medically significant or life-threatening consequences; unable to perform ADL. | - Hold ICPI until symptoms resolve to baseline with appropriate supplementation.  
- Endocrine consultation.  
- May admit for IV therapy if signs of myxedema (bradycardia, hypothermia).  
- Thyroid supplementation and reassessment as in G2. |

*American Society of Clinical Oncology Clinical Practice Guideline*
## Hyperthyroidism

<table>
<thead>
<tr>
<th>Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1: Asymptomatic or mild symptoms.</td>
<td>- Can continue ICPI with close follow-up and monitoring of TSH, FT4 every two to three weeks until it is clear whether there will be persistent hyperthyroidism (refer below) or hypothyroidism (refer to 4.1.1).</td>
</tr>
<tr>
<td>G2: Moderate symptoms; able to perform ADL.</td>
<td>- Consider holding ICPI until symptoms return to baseline.</td>
</tr>
<tr>
<td></td>
<td>- Consider endocrine consultation.</td>
</tr>
<tr>
<td></td>
<td>- Beta-blocker (e.g., atenolol, propranolol) for symptomatic relief.</td>
</tr>
<tr>
<td></td>
<td>- Hydration and supportive care.</td>
</tr>
<tr>
<td></td>
<td>- Corticosteroids are not usually required to shorten duration.</td>
</tr>
<tr>
<td></td>
<td>- For persistent hyperthyroidism (&gt;6 weeks) or clinical suspicion, work-up for Graves’ disease (TSI or TRAb) and consider thionamide (methimazole or PTU).</td>
</tr>
<tr>
<td></td>
<td>- Refer to endocrinology for Graves’ disease.</td>
</tr>
<tr>
<td>G3 to 4: Severe symptoms; medically significant or life-threatening consequences; unable to perform ADL.</td>
<td>- Hold ICPI until symptoms resolve to baseline with appropriate therapy.</td>
</tr>
<tr>
<td></td>
<td>- Endocrine consultation.</td>
</tr>
<tr>
<td></td>
<td>- Beta-blocker (e.g., atenolol, propranolol) for symptomatic relief.</td>
</tr>
<tr>
<td></td>
<td>- For severe symptoms or concern for thyroid storm, hospitalized patient and initiate prednisone 1 to 2 mg/kg/day or equivalent tapered over one to two weeks; consider also use of SSKI or thionamide (methimazole or PTU).</td>
</tr>
</tbody>
</table>

American Society of Clinical Oncology Clinical Practice Guideline
Hyperthyroidism

• Graves’ disease is usually persistent and should be considered if hyperthyroidism lasts >5-6 weeks
• Ophthalmopathy and thyroid bruit are suggestive of Graves’ disease
• The thyrotoxic phase of thyroiditis is the most common cause of hyperthyroidism in patients treated with ICI
  • Usually resolves within a 2-4 weeks to normal or hypothyroidism
  • Should be monitored closely for progression to hypothyroidism, with labs at least every 2-3 weeks
  • Symptomatic management with a beta-blocker can be used
Iyer et al.

Immune-Related Thyroiditis with Immune Checkpoint Inhibitors
Iyer et al.

• 657 patients treated with ICI during study period
  • Patients with preexisting thyroid disease, hypothyroidism without thyrotoxic phase, hyperthyroidism 2/2 Graves’ diseases or toxic nodule were excluded
• 43 patients met inclusion criteria
Iyer et al.
• 14/43 patients (33%) were symptomatic in thyrotoxic phase
• 37/43 (84%) developed hypothyroidism requiring levothyroxine treatment
• 4/43 (9%) patients recovered from transient hypothyroidism without levothyroxine
  • All 4 of these patients received steroids for other reasons (for chemotherapy or other irAEs)
• 2/43 patients died before they could develop hypothyroidism
• 5/37 (12%) patients were symptomatic during the hypothyroid phase
### Table 2. Effect of Steroid Exposure and Elevated Thyroid Antibodies on Levothyroxine Dose

<table>
<thead>
<tr>
<th>Antibody and steroid exposure versus dose</th>
<th>&lt;1 μg/kg (n=10)</th>
<th>1–1.6 μg/kg (n=17)</th>
<th>&gt;1.6 μg/kg (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab+/steroid+, (n)</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Ab+/steroid−, (n)</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Ab−/steroid+, (n)</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Ab−/steroid−, (n)</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 3. Timeline of Thyroiditis Depending on Individual Drug Regimen

<table>
<thead>
<tr>
<th>Timeline (weeks)</th>
<th>Pembrolizumab (n=9)</th>
<th>Nivolumab (n=14)</th>
<th>Ipilimumab + nivolumab (n=17)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to thyrotoxicosis</td>
<td>5 [3.15–6.84]</td>
<td>6 [3.58–8.41]</td>
<td>2 [1.19–2.8]</td>
<td>0.423</td>
</tr>
<tr>
<td>Thyrotoxicosis phase</td>
<td>5 [3.61–6.38]</td>
<td>10 [8.18–11.81]</td>
<td>6 [4.07–7.92]</td>
<td>0.05</td>
</tr>
<tr>
<td>Time to hypothyroidism</td>
<td>10 [8.61–11.38]</td>
<td>17 [8.82–25.18]</td>
<td>10 [8.11–11.90]</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Data shown are median [confidence interval].
Iyer et al.

- Thyroiditis related to ICI seems to be more commonly associated with anti-PD1 drugs used alone or in combination with anti-CTLA-4 agents.
- Onset of hypothyroidism was significantly more rapid in patients treated with combined ipilimumab and nivolumab (10 weeks) than with nivolumab alone (17 weeks).
- Patients in this study were followed for 14 months, all the patients started on levothyroxine remained on this with normal TFTs at their last follow-up.
Baseline TFTs (TSH and free T4) prior to starting ICI

Thyrotoxicosis due to immune-related thyroiditis suspected

Symptoms
- palpitations, heat intolerance, tremors, anxiety, diarrhea, etc.
- may be masked if on beta blockers

OR

Routine TFTs (TSH and free T4) monitoring before each ICI cycle (typically 2-4 weeks intervals)

Check TSH, free T4

Low TSH with normal or high free T4

ENDOCRINOLOGY CONSULTATION
- Check for preexisting hypothyroidism adjust thyroid hormone doses
- Rule out other causes of thyrotoxicosis
- Additional labs: total T3, TPO, TSI, TRAb
- Additional images: US thyroid/RAIUS/Tc scan

Thyrotoxicosis due to immune-related thyroiditis confirmed

TREATMENT
- Beta blockers if symptomatic
- Immunotherapy hold if ≥ CTCAE grade 3 and restart when ≤ grade 1
- Immunotherapy discontinuation not recommended
- Steroids not routinely recommended

FOLLOW UP
- Close monitoring for symptoms
- Thyroid function testing every 2 weeks
- Start thyroid hormone when hypothyroid (low free T4, even if TSH is not high) and then follow per standard hypothyroidism guidelines
Back to our patient

• Our patient had persistent hyperthyroidism after 5-6 weeks so patient was started on methimazole 30mg daily and propranolol 20mg Q8H with improvement in symptoms
• Patient is scheduled for Endocrinology clinic follow up
• Per Oncology, nivolumab is being held for now
Objectives

• Review the endocrine related adverse effects associated with immune checkpoint inhibitors
• Discuss the range of thyroid dysfunction induced by immune checkpoint inhibitors
• Discuss the management of thyroid disorders associated with immune checkpoint inhibitors
References

- Uptodate, Patient selection criteria and toxicities associated with checkpoint inhibitor immunotherapy.
- Fejzo, M.S., et al., Genetic analysis of hyperemesis gravidarum reveals association with intracellular calcium release channel (RYR2). Molecular and Cellular Endocrinology 2016.
- Sznol, M. Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management. Cancer Treatment Reviews 58 (2017) 70–76.
- Ferrari, S. M. Thyroid disorders induced by checkpoint inhibitors. Endocrine and Metabolic Disorders 2018.