Endocrinopathies with Immune Checkpoint Inhibitors; a 36F with Metastatic Melanoma

Isabel Casimiro, MD PhD
Feb 2017
• 35 yo F with no significant PMH
• Hx of 2 moles on her L posterior arm for many years
• One of her moles "fell off" and bled then “grew back, was really hard”
• Biopsy: nodular melanoma
• Depth of 2.2mm, presence of ulceration, mitotic rate of 12/mm², and 1/3 sentinel lymph nodes positive
• Late April 2016 CT c/a/p w & MRI Brain wwo: No metastatic disease
• 5/11/16 : Underwent left complete Level 3 axillary lymph node dissection (0/28)
• Diagnosed with stage IIIB malignant melanoma metastatic to L axillary sentinel LN
• Recs: ipilimumab (anti-CTLA4) vs pembrolizumab (anti-PD-1)
Anti-CTLA4 mAbs

- CTLA4 is an immune checkpoint molecule expressed on T cells
- Down regulates T cell activation after T cell/APC interaction
- Ipilimumab (Yervoy) & tremelimumab are mAbs directed against CTLA4
  - Blocks it to promote anti tumor immunity
• Randomized Phase 3 study in which ipilimumab with or without gp100 was given compared to gp100 alone as control

• Standard of care for metastatic melanoma is enrollment in clinical trial

• gp100 is a cancer vaccine that induces immune responses but has limited anti tumor activity
676 patients enrolled:

- 403 randomly assigned to receive ipi + gp100
- 137 ipi alone
- 136 gp100 alone (control group)

Ipilimumab dose: 3mg/kg x 4 doses

NEJM 2010;363:711-723
Overall median survival was 10 months among patients receiving ipi + gp100 (95% CI, 8.5-11.5), as compared to 6.4 mos among patients receiving gp100 alone (95% CI, 5.5-8.7).

676 patients enrolled:
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NEJM 2010;363:711-723
Ipilimumab for Metastatic Melanoma Treatment

- 2011 US FDA approves ipilimumab for advanced melanoma
- Survival benefit results were not obtained with tremelimumumab
- Approved dose is 3mg/kg IV infusion Q3wks for 4 doses total; maintenance therapy can continue for some patients
- Toxicity profile worsens in a dose dependent manner
Immune Related Adverse Events (IRAEs)

- In a pooled analysis of 325 patients treated with 10mg/kg ipilimumab Q3 weeks for 4 doses IRAEs were observed in 72.3%

- IRAEs: colitis/diarrhea, dermatitis, hepatitis, endocrinopathies
Endocrine-Immune Related Adverse Events (E-IRAEs)

- E-IRAEs: hypopituitarism (caused by hypophysitis), thyroid disease, abnormalities in TFTs, primary adrenal insufficiency
- Incidence of anti-CTLA4 hypophysitis was dose dependent
  - 1-3mg/kg occurred in 1.8-3.3% cases
  - >3mg/kg occurred from 4.9-17% of cases
- Primary adrenal insufficiency has been reported (0.3-1.5%)
Presentation of anti-CTLA4 Hypophysitis

- Nonspecific symptoms: fatigue, weakness, headache, nausea, vertigo, behavior change, visual impairments such as diplopia, confusion, memory loss, loss of libido, anorexia, insomnia, hallucinations, temperature intolerance, subjective f/c

- Average onset: 6-12 weeks after initiation of therapy

- Levels of ACTH, cortisol, TSH, FT4, GH, prolactin, IGF-1, FSH, LH & testosterone (in males) are variably altered

- Most cases: MRI reveals enlargement of pituitary gland (60-100%), & thickening of the stalk

- Height in sagittal view increases from 3.4 - 6mm to 7.7 - 11.8mm
Figure 2: MRI Findings in a Patient With Ipilimumab-Induced Hypophysitis — These MRI images show the pituitary gland before therapy (A) and after four cycles of induction (B).
Clinical Approach to Pt with Hypophysitis

- Pituitary MRI and pituitary function assessment
- If anti-CTLA4 hypophysitis is confirmed, the drug should be held and IV glucocorticoids should be given for a few days
- Followed by oral glucocorticoids with tapering to replacement doses
- Once hypophysitis resolves with treatment and adequate hormone replacement has been tailored anticancer treatment can be resumed with close monitoring of pituitary function
Treatment of anti-CTLA4-mAb Hypophysitis

- Most Pts experience resolution of symptoms a few days after withdrawal of the drug and the start of high dose glucocorticoids, LT4 & sex hormone replacement

- Time time needed for resolution of symptoms & duration of replacement therapy may be longer or even lifelong (considering limited survival of Pts)
Thyroid Side Effects by anti-CTLA4 mAbs

- Second most frequent endocrine organ involved in anti-CTLA4-mAb toxicity
- Incidence is 0-4%
- Presents as thyroiditis usually associated with antthyroglobulin & anti-TPO Ab positivity & hypothyroidism, or transient hyperthyroidism
- Most cases have a subclinical course, may be transient or may evolve into permanent hypothyroidism
- Rare cases of Graves opthalmopahy have been reported with elevation of TSH receptor antibodies but normal thyroid function
Mechanism of CTLA-4 mAb Induced Hypophysitis?

• Pathogenesis is attributable to autoimmunity, however, the exact mechanism remains to be clarified

• anti-CTLA-4 mAbs may act by depleting T reg cells vs antibodies directed against the pituitary gland (presence of pituitary antibodies remains to be shown)
Other Immune Checkpoint Inhibitors: anti-PD-1 mAbs
PD-1 mAbs

- PD-1 is another immune checkpoint inhibitory receptor expressed on activated T cells to inhibit T cell activation and proliferation, thereby promoting immunological self tolerance
- Highly expressed on T cells from patients with tumors causing tumor related immune suppression
- Pharmacological interference with anti-PD-1 and anti-PD-1L increases anti tumor immunity & enhances immunity in vitro
- PD-1 inhibitors: Pembrolizumab (Keytruda) & Nivolumab (Opdivo)
- mAbs blocking PD-1 have been shown to be beneficial in different types of cancers (H&N cancer, ovarian, bladder, Hodgkin’s lymphoma, melanoma, RCC, non-small cell lung cancer)
Complete response in a patient with melanoma who received 3mg/kg of anti-PD-L1 antibody

Circles indicate an initial increase in the size of pulmonary nodules at 6 weeks and 3 months, followed by complete regression at 10 months (immune related pattern of response)
Anti-PD-L1 Endocrine Side Effects

- Phase I study of 207 patients with advanced cancers
- No Pt developed hypophysitis
- Endocrine side effects developed in Pts receiving higher doses of drug (3-10mg/kg)
  - 6 Pts (3%) developed hypothyroidism
  - 2 Pts (1%) developed autoimmune thyroiditis
  - 3 Pts (1.5%) developed adrenal insufficiency
- In one retrospective study in Pts receiving Ipilimumab incidence of thyroiditis/hypothyroidism was reported at 6% whereas it was 22% in group receiving both ipilimumab & nivolumab
<table>
<thead>
<tr>
<th>Case #</th>
<th>Previous History of Thyroid Disease</th>
<th>Tg (1.3–31.8 ng/ml)</th>
<th>Anti-Tg (0–4 IU/ml)</th>
<th>Anti-TPO (&lt;60 units/ml)</th>
<th>TSI (&lt;123%)</th>
<th>Imaging at Thyroid Abnormality</th>
<th>Status of Hypothyroidism (at 6 months)</th>
<th>Tumor Response</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Subclinical Hypothyroidism on natural thyroid</td>
<td>109×33</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>US: decreased vascularity</td>
<td>Resolved at 6 weeks</td>
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<td>2</td>
<td>None</td>
<td>N/A</td>
<td>24× 2.4</td>
<td>Neg</td>
<td>161×96</td>
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<td>Persistent</td>
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<td>None</td>
<td>162.6×4</td>
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<td>Neg</td>
<td>164×99</td>
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<td>4</td>
<td>None</td>
<td>154 × 20</td>
<td>Neg</td>
<td>Neg</td>
<td>N/A</td>
<td>RA: decreased uptake</td>
<td>Resolved at 2 months</td>
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<td>5</td>
<td>None</td>
<td>141 × 1.3</td>
<td>Neg</td>
<td>Neg</td>
<td>128×87</td>
<td>US: diffusely hypoechoic</td>
<td>Persistent</td>
<td>Yes</td>
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<td>6</td>
<td>Resolved Hypothyroidism</td>
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<td>8.6×2.1</td>
<td>1300×1400</td>
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<td>N/A</td>
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<tr>
<td>7</td>
<td>Hypothyroidism on LT4 25μg daily</td>
<td>N/A</td>
<td>247×108</td>
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<td>150×103</td>
<td>US: diffusely hypoechoic gland</td>
<td>Persistent</td>
<td>Yes</td>
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</table>
Hypothyroidism in Pts receiving anti-PD1 agents (10 cases)

- During thyroiditis phase, 50% of Pts had elevated Tg titers, 40% had elevated anti-Tg, and 40% had elevated TSI
- Permanent hypothyroidism was noted in 80% of cases
- Hypothyroidism following initiation of immune therapy has immunologic and non-immunologic mediated mechanisms and is likely to be persistent
Mechanism of PD-1 Associated Hypothyroidism

• Immunologic phenomenon?

• Destructive thyroiditis with release of thyroid antigen and consequent secondary antibody production?
  • Initial hyperthyroid phase was notable for elevated Tg levels in all the patients who did not have anti-Tg as well as elevated anti-Tg and TSI in 40 & 50% of Pts respectively

• Evidence of thyroiditis in Pts with available imaging

• Subsequent normalization of Tg and disappearance of anti-thyroid antibodies support a destructive process ending in permanent hypothyroidism in most patients

• Presence of anti-TPO was not necessary for development of hypothyroidism
Patient Course

- Started on Ipilimumab (anti-CTLA4) on 8/2/16 plan for 4 infusions (3mg/kg)
- After 3rd cycle, began to feel run down, tired, & dizzy upon waking

Labs 10/4/16 07:06am

- Cortisol <0.4
- TSH: 0.02
- FT4: 0.61
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Labs 10/4/16 07:06am

Cortisol <0.4
TSH: 0.02
FT4: 0.61

Oncologist started on 20mg HC Qd & 25mcg LT4 Qd
<table>
<thead>
<tr>
<th></th>
<th>Prior to Ipi</th>
<th>After 1st cycle</th>
<th>After 2nd cycle</th>
<th>After 3rd cycle</th>
<th>Endo Appt</th>
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<tbody>
<tr>
<td>THYROID FUNCTION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Triiodothyronine, ...</td>
<td></td>
<td></td>
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<td></td>
<td>224</td>
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<tr>
<td>Thyroxine, Free</td>
<td></td>
<td>1.24 *</td>
<td>1.32 *</td>
<td>0.93 *</td>
<td>0.61*</td>
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<tr>
<td>Thyroglobulin Ab</td>
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<td>&lt;0.4</td>
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<tr>
<td>Thyroid Perox. Ab</td>
<td></td>
<td>1.16</td>
<td>1.26</td>
<td>0.43</td>
<td>0.02</td>
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<tr>
<td>Thyrotropin</td>
<td></td>
<td></td>
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<td></td>
<td>0.01</td>
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</table>
Labs 10/25/16 07:54am:
cortisol: 30.4
estradiol (high sensitivity): <3
FSH: 4.7
LH: 2.5
Prolactin <1
ACTH: 1.2
IGF-1: 75 (54-258 ng/mL)
hGH: 0.10
Labs 10/25/16 07:54am:

- Cortisol: 30.4
- Estradiol (high sensitivity): <3
- FSH: 4.7
- LH: 2.5
- Prolactin <1
- ACTH: 1.2
- IGF-1: 75 (54-258 ng/mL)
- hGH: 0.10

-HC changed to 15mg QAM & 5mg QPM
-LT4 increased to 137 mcg
-Advised to start OCPs
-Referral to Reproductive Endo given desire for pregnancy
Further Course

- Received 4 cycles of Ipilimumab 3mg/kg (Aug-Oct 2016)
- 1/6/17 CT Chest showed interval development of pulmonary nodules & metastatic disease in sternum
- Added Nevilomab on 1/26/17 (in conjunction with 2nd round of Ipilimumab infusions), got 1st cycle of both drugs

- Admitted on 2/14/17 with Hg 2.9 and hypotension 80/40s when she presented for 2nd ipi/Nevilomab infusions

- Anemia thought to be due to MAHA vs HLH, discharged after several transfusions and treatment with high dose steroids

- Unclear if she will be continued on chemotherapy at this time
Conclusions

• Hypophysitis has emerged as distinctive side effect of CTLA-4 blocking antibodies

• Endocrine disease experienced by patients treated with ipilimumab includes mostly hypophysitis, and more rarely thyroid disease, occasional AI

• Hypothyroidism following initiation of immune therapy, has been seen with use of anti-PD-1 Abs & has immunologic and non immunologic mediated mechanisms and is likely to be persistent


• Ascierto & Marincola. 2015: The Year of Anti-PD-1/PD-L1s Against Melanoma and Beyond

Objectives

- To learn about the anti-CTLA4 monoclonal Abs in the treatment of metastatic melanoma

- To discuss the most common endocrinopathies associated with immune checkpoint inhibitors