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Evaluation and Management of Suspected Immune-Mediated Endocrine Toxicities

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THYROID DYSFUNCTION

PRESENTATION
Patient presents with new onset symptoms of hyperthyroidism, hypothyroidism, or abnormal TSH, free T4, or total T3 levels 1 week after immune checkpoint inhibitor (ICI) initiation and up to 12 months after initiation. Majority of cases occur within 15 weeks.

ASSESSMENT

TSH low with high T4 or T3
- Thyrotoxicosis:
  - Rule out adrenal insufficiency if patient is symptomatic
  - Endocrinology consult/referral
  - Beta blockers, if symptomatic
  - Hold ICI if CTCAE grade 3+ or Graves' disease
  - Follow TSH and free T4 every cycle

TSH high with normal or low T4 or T3
- Primary hypothyroidism:
  - Rule out adrenal insufficiency if patient is symptomatic prior to starting thyroid hormone therapy
  - If TSH > 10 mU/L, start levothyroxine per standard guidelines
  - Adjust dose every 6 weeks

TSH low/normal with low T4 or T3
- Central hypothyroidism:
  - Evaluate for hypophysitis, see Page 3
  - Endocrinology consult/referral

TFT = thyroid function test
TSH = thyroid stimulating hormone
TSI = thyroid stimulating immunoglobulin

1 Symptoms include palpitations, tachycardia or tremors
2 Symptoms fatigue, weight gain, or cold intolerance
3 PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA-4 inhibitor (ipilimumab)

TREATMENT

Assess for Graves' disease versus thyroiditis:
- Check total T3, TSH receptor Ab, and TSI
- I-123/Tc uptake and scan

Monitor for development of hypothyroidism with TSH and free T4 every 2-6 weeks or with every cycle for the next 3-4 months
- Labs consistent with primary hypothyroidism?
  - Yes
    - Primary hypothyroidism: Start levothyroxine treatment
  - No
    - Resume routine thyroid function tests monitoring per package insert or with every cycle
    - Resume ICI if previously held

Graves' disease
- Hold ICI until hyperthyroidism is controlled
- Endocrinology evaluation to initiate methimazole
- Consider definitive therapy with radioactive iodine or surgery if indicated

Thyroiditis
- Low or normal uptake indicates thyroiditis. High uptake is usually seen with Graves' disease or hot nodule. Uptake scan is contraindicated if IV contrast within 2 months or patient is on amiodarone.
- Start levothyroxine at 1.2-1.6 mcg/kg/day in young or healthy patients. For patients age > 60, or those with known heart disease, consider starting at 50 mcg daily and titrate dose based on response

Labs consistent with primary hypothyroidism?
- Yes
- No

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### HYPOPHYSITIS PRESENTATION

After immune checkpoint inhibitor (ICI)\(^1\) initiation:
- Patient presents with new onset of headache, sinus pressure, fatigue or
- Patient is asymptomatic and has incidental laboratory findings or MRI findings concerning for hypophysitis
- Incidental findings consist of any of the following:
  - Low T4 with low/normal TSH
  - Low ACTH level with normal or low cortisol
  - MRI findings consistent with hypophysitis

### ASSESSMENT

Severe of life-threatening symptoms\(^2\) or adrenal crisis?

- Yes
  - Hold ICI
  - Admit to Acute Cancer Care Center (ACCC) or transfer to local Emergency Department
  - Draw urgent labs\(^3\)

- No
  - Urgent Endocrinology consult with provider-to-provider communication
  - Check labs if not already done: TSH, free T4 and total T3, ACTH, and cortisol
  - MRI pituitary with and without contrast
  - Check testosterone, FSH, and LH in men, and estrogen levels, and FSH, LH in premenopausal women

ACTH = adrenocorticotropic hormone
FSH = follicle-stimulating hormone
LH = luteinizing hormone
TSH = thyroid stimulating hormone

\(^1\) CTLA-4 inhibitor (ipilimumab) single agent or in combination with other systemic anticancer therapies

\(^2\) Severe or life-threatening symptoms include hypotension, persistent nausea/vomiting, extreme fatigue, hyponatremia

\(^3\) Blood draw for ACTH, cortisol, TSH, total T3, Free T4 need to be done BEFORE administration of high dose steroids.

Cortisol assay will not be reliable if patient has received most steroids (hydrocortisone, prednisone, methylprednisolone).

### TREATMENT

#### Acute management of adrenal crises with IVFs and high dose steroids as follows:
- Infuse 2-3 liters of 0.9% normal saline (NS) or 5% dextrose in isotonic saline (D5NS) as quickly as possible. Ensure frequent hemodynamic monitoring.
- Hydrocortisone 100 mg IV for 1 dose, then 50 mg IV every 6-8 hours for 24 hours

#### Severe headache or vision changes?

- Yes
  - Replace deficient hormones:
    - Physiologic hydrocortisone replacement orally\(^5\)
    - Levothyroxine replacement
    - Reassess testosterone/estradiol at follow-up\(^6\)
    - Resume ICI when patient is asymptomatic and on stable doses of hydrocortisone

- No
  - Hold ICI until acute symptoms resolve and patient is started on stable replacement doses of hormones (physiological doses of steroids and/or thyroid hormone)

#### Hypophysitis confirmed:

- Hold ICI until acute symptoms resolve and patient is started on stable replacement doses of hormones (physiological doses of steroids and/or thyroid hormone)

#### Hypophysitis not confirmed:

- Further evaluation by Endocrinology

\(^4\) ACTH deficiency: low cortisol with low or normal ACTH. TSH deficiency: low free T4 with low or normal TSH

\(^5\) Hydrocortisone 10 mg/m\(^2\) BSA per day (in general, 15 mg in the morning and 5 mg at 3 PM)

\(^6\) Treatment of testosterone and estrogen deficiencies based on clinical indications

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DIABETES

PRESENTATION
Patient without history of diabetes presents with new onset grade 2\(^1\) hyperglycemia or patient with type 2 diabetes (T2DM) presents with worsening glucose control\(^2\) after immune checkpoint inhibitor (ICI)\(^3\) initiation and up to 12 months after last dose of ICI

ASSESSMENT

- Check BMP, glucose, and C-peptide levels
- Check urinalysis (UA) for ketones
- Laboratory findings consistent with DKA\(^4\)?

TREATMENT

A: Urgent Endocrinology-Diabetes consult\(^6\)
- Is C-peptide < 1 ng/mL?
  - No
    - Routine Endocrinology-Diabetes consult/referral
      - Intensify diabetes regimen
      - Continue ICI
  - Yes
    - Hold ICI
    - Start a basal/bolus insulin therapy
    - Check antibodies\(^8\)
    - Diabetes education

B: See box A on this page
- Is patient still having glucose values > 250 mg/dL after 2 weeks of intensifying regimen?
  - Yes
    - Reassess C-peptide and glucose levels in 4-6 weeks
    - Resume ICI once stable on insulin therapy
    - Continue diabetes education and insulin dose adjustments
  - No
    - See box B on this page

1. Grade 2 hyperglycemia as defined by CTCAE as fasting glucose more than 160-250 mg/dL.
2. Worsening glycemic control is defined as change in baseline control of diabetes prior to initiation of ICI with glucose values consistently above 250 mg/dL despite compliance with medication regimen
3. PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA-4 inhibitor (ipilimumab)
4. Labs suggestive of DKA: blood glucose > 250 mg/dL, anion gap > 14, arterial pH < 7.3 or bicarbonate < 18 mEq/L, and moderate ketonuria or ketonemia [Note: Blood glucose may be lower than expected in patients on SGLT-2 inhibitors (e.g., empagliflozin, canagliflozin)]
5. If admitted to MD Anderson, treat according to Hyperglycemic Emergency Management (DKA/HHS/EDKA) - Adult algorithm. For patients at outside facilities, direct communication with the admitting service is needed to ensure the patient is discharged on basal/bolus insulin therapy is recommended.
6. If outpatient page “Endocrinology-Diabetes Consult-Outpt” on the On-Call Calendar for a same day diabetes consultation
7. Based on clinical judgement, but new onset diabetes, dramatic worsening, and low or inappropriately normal c-peptide levels are suggestive
8. Glutamic acid dehydrogenase-65 antibody, islet antigen-2 antibody, anti-insulin antibody, and zinc transporter 8 antibodies
APPENDIX A: Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

Endocrine Disorders

<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate symptoms; medical intervention indicated</td>
<td>Severe symptoms; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; thyroid replacement indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Abnormal glucose above baseline with no medical intervention</td>
<td>Change in daily management from baseline for a diabetic; oral anti-glycemic agent initiated; workup for diabetes</td>
<td>Insulin therapy initiated; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

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SUGGESTED READINGS


Thyroid Dysfunction


Hypophysitis


Diabetes


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DEVELOPMENT CREDITS

This practice consensus statement is based on majority opinion of the Endocrine Toxicities experts at the University of Texas MD Anderson Cancer Center for the patient population. These experts included:

Core Development Team Leads
Sonali Thosani, MD (Endocrine Neoplasia and HD)

Workgroup Members
Conor Best, MD (Endocrine Neoplasia and HD)
Naifa Busaidy, MD (Endocrine Neoplasia and HD)
Ramona Dadu, MD (Endocrine Neoplasia and HD)
Wendy Garcia, BS*
Amy Pai, PharmD*

*Clinical Effectiveness Development Team