Endocrine Toxicities

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Disclosures

• None
Endocrinopathies

- Occurs in 10-40% of patients receiving ICI

- Can present with symptoms of hormone deficiency, hormone excess or both

- Spectrum of clinical presentations ranges from no symptoms to severe life-threatening symptoms
  - Often vague and overlap with common cancer related symptoms
Endocrinopathies

Differ from other irAEs

• Use of high dose steroids do not appear to decrease the severity or duration
• Generally, do not require discontinuing ICI
• Management is based around replacement of the underlying deficiency
• Tend to result in chronic conditions and require lifelong therapies
Pituitary Hypophysitis

Case
• 71M with stage M1c melanoma s/p 4 cycles ipi + nivo c/b mild rash/pruritus managed conservatively

• 3 days after receiving C4, he reported mild nausea and a “wicked” headache

• Had been started on metformin for hyperglycemia; attributed to med. Held for a few days with improvement, but persistent H/A, and now notable fatigue, loss of appetite, general malaise

• Labs and bMRI arrange
<table>
<thead>
<tr>
<th>Component</th>
<th>Ref Range</th>
<th>11/23</th>
<th>12/14</th>
<th>12/21</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.40 - 5.00 uIU/mL</td>
<td>1.25</td>
<td>0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>fT4</td>
<td>0.9 - 1.8 ng/dL</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
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<tr>
<td>T3</td>
<td>60 - 181 ng/dL</td>
<td>75</td>
<td>84</td>
<td></td>
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<tr>
<td>Testosterone, Total</td>
<td>249 - 836 ng/dL</td>
<td></td>
<td>&lt;12</td>
<td></td>
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<tr>
<td>Cortisol</td>
<td>Ug/dL</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NA</td>
<td>134 - 145 mmol/L</td>
<td>132</td>
<td>133</td>
<td>129</td>
</tr>
<tr>
<td>K</td>
<td>3.4 - 5.0 mmol/L</td>
<td>4.3</td>
<td>4.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Creat</td>
<td>0.60 - 1.50 mg/dL</td>
<td>0.87</td>
<td>1.07</td>
<td>1.11</td>
</tr>
</tbody>
</table>

Labs and sx suggestive of hypophysitis; he was started on 10mg prednisone
• H/A nearly resolved after 1 dose of prednisone

• Pituitary MRI revealed new diffuse gland enlargement with heterogeneous enhancement compared to a pre-tx MRI

• Prednisone reduced to 5mg once daily, referred to Endocrine
Hypophysitis

• Immune mediated inflammation of the pituitary gland
• Incidence
  • anti-CTLA-4: 1.8 - 18%
  • anti-PD-1/PD-L1: 0.3 - 1.2%
  • anti-CTLA-4 + PD-1/PD-L1: 7 - 10%
• Median onset: 12 weeks (3-76w)
  • hypophysitis due to PD-1/ PD-L1 tends to occur later than in CTLA-4 and is more likely to involve a single hormonal axis

Wright and Johnson, 2023, J Clin Endocrinol Metab, 108, 1514-1525
Percik et al, 2023, Endocrine Connections, 12 e220513
Hypophysitis

• Typically involves the anterior pituitary

• Clinical s/sx are the result of:
  • Primary hormone deficiencies, (most commonly TSH, followed by ACTH)
    • Fatigue (59-73%)
    • Nausea
    • Anorexia
  • Mass effect of the pituitary gland
    • Headache (32-87%)
    • Rarely, visual field defects

Wright and Johnson, 2023, *J Clin Endocrinol Metab*, 108, 1514-1525
Spagnola et al, 2022, *Cancers*, 15, 246
Pituitary Evaluation:

• Baseline screening is controversial
• Labs
  • AM cortisol & ACTH, TSH, fT4, electrolytes
  • Consider LH and testosterone in males and estrogen in symptomatic females
  • Cort-stim for indeterminate results (AM cortisol > 3 and < 15)
  • Progressive decline in TSH may be indicative of developing pituitary dysfunction

• Medication reconciliation
  • Opioids, megestrol acetate can affect pituitary function

• Imaging
  • Brain MRI (pituitary protocol) in all patient with new hormonal deficiencies, severe H/A, or vision changes
    • Need to R/O brain metastases
    • Only ½ will see radiologic signs on
Management

• Continue ICI (or temporary hold)

• Replacement of affected hormone(s) due to secondary hypothyroidism or secondary adrenal insufficiency

• High doses of steroids are not necessary and have been associated with worse outcomes
  • Short course may be necessary for those sx from mass effect

• Monitor thyroid function with fT4 for those with central hypothyroidism (↓ TSH, ↓fT4)
Case summary

• Diagnosis
  • Hypophysitis
  • TFTs showed mild thyrotoxicosis which resolved without LT4 tx
  • Testosterone level improved to low normal

• Plan
  • 5mg prednisone daily

• Outcome
  • Completed two year of immunotherapy with near CR

• Education
  • Sick day dosing
  • Vigilance monitoring for additional irAEs
  • Likely lifelong replacement
Case

• 85 active male, w/ metastatic cuSCC s/p 4 cycles pembrolizumab 400mg with near CR

• 2 mo after treatment completion he underwent a rather extensive outpatient procedure to excise another SCC- requiring skin graft.

• Shortly thereafter developed weakness, malaise, decreased appetite- big change from baseline.

• Presented to local ED: evaluation unrevealing, received IVH, felt better, D/C home

• Syncopal event the next day with increased lethargy and confusion. anorexia. Family called EMS. Hypotensive on arrival to ED.

• Received IVH, empiric IV abx for possible UTI. Some improvement while hospitalized. D/C home with PT/OT.
• Family contacted office to report events, Given ongoing poor PS and such a change from baseline, suspicion for endocrine tox, specifically AI, either primary or central.

• Random cortisol low. ACTH obtained but pending.

• Empirically started on 10mg prednisone with dramatic and rapid improvement in symptoms.

• Referred for formal endocrine consult; cort stim and pituitary MRI to confirm diagnosis
  • Cort stim: 0.5, 1.9, 3.0
  • ACTH undetectable
  • Pituitary MRI 7/31/23 appears normal and w/o an obvious change from prior head CT
Case - summary

• Diagnosis
  • Adrenal Insufficiency
  • Testing of other axes normal: testosterone, prolactin, IGF-1, TSH/FT4.

• Plan
  • 10mg prednisone daily; later reduced to 5mg daily

• Outcome
  • Ongoing near CR
  • Repeat cort stim in ~ 6 months

• Education
  • Sick day dosing
  • Vigilance monitoring for additional irAEs
  • Likely lifelong replacement
Education

Stress dosing: patient AND caregiver(s)

• Sick days Periop / dental procedures
• Medical alert bracelet/necklace
• Adrenal crisis
• Use of emergency steroid injectables (IM hydrocort)