Introduction

Oncological immunotherapy is a broad term encompassing any therapy designed to increase immune system activity against cancer cells. Immune checkpoints are small molecules which maintain immune homeostasis through positive and negative signaling. Immune Checkpoint Inhibitors (ICPis) are a subgroup of monoclonal antibodies which target these molecules to activate immune system function with the goal of increasing anti-tumor activity. Two prevalent ICPis are Ipilimumab (Yervoy) which binds to cytotoxic T lymphocyte-associated antigen 4 receptor (CTLA-4) and Nivolumab (Opdivo) which binds to programmed death-1 receptor (PD-1).

ICP toxicity can trigger autoimmune effects called immune-related adverse events (irAEs). These most commonly include dermatitis, hepatitis, colitis, myositis, and endocrine abnormalities. Less common but potentially more severe irAEs include neuritis, pneumonitis, myocardiitis, renal injury, and hematologic toxicity. ICPs are becoming the standard of care for a number of indications and thus recognition and prompt treatment of potentially life-threatening irAEs becomes increasingly important.

Case History

55 year old male presented to Maine Medical Center with one week of vague systemic complaints including dizziness, fatigue, headaches, diffuse arthralgias, daily nausea and vomiting, and six pound weight loss.

Past Medical and Surgical History
- Adrenal cortical carcinoma diagnosed in 2009
- Subsequent right adrenalectomy with nephrectomy
- Multiple rounds of chemotherapy and radiation
- Recurrent mets in 2013 required resections of the liver, diaphragm, and chest wall
- Biopsy confirmed recurrence in 2018 in left supravclavicular lymph nodes
- Started on Ipilimumab and Nivolumab immunotherapy one month prior to this presentation to Maine Medical Center.

Additional home medications
- Mitostate 1,500mg nightly
- Lorazepam 0.5mg q4H PRN

Social history
- No known drug allergies
- Never smoker
- One alcoholic drink per week

Physical Exam and Pertinent Labs

BP 107/74 (Sitting) | Pulse 80 | Temp 36.3 °C | Resp 16 | SpO2 98%

HEENT: No scleral icterus. Mucous membranes moist.

Neck: Full painless ROM. No appreciable lymphadenoapathy or thymogemaly.

Cardiovascular: Regular rate and rhythm. No murmurs or rubs.

Chest: Clear to auscultation bilatally.


Extremities: Diffuse arthralgias, joints are tender to movement without edema or erythema.

Neurological: CN II-XII grossly intact. Ambulating independently but dizzy with standing. No ataxia or tremor.

Skin: No rashes or lesions.

CBC: normal

BMP: normal

Calcium: 9.5

APT: 104 (39 – 117)

AST: 82 (0 – 40)

ALT: 186 (10 – 47)

Bilirubin: 0.4

TSH: -0.02

Free T4: >8

Prolactin: 22.3 (4.1 – 18.4)

FSH: 63.5 (1.5 – 12.4)

LH: 73.7 (1.7 – 8.3)

Testosterone, total: 1,215 (250 – 1,100)

Assessment, Hospital Course, and Treatment

- Symptoms and labs reflected immunotherapy toxicity manifesting as several irAEs including:
  - Hypophysitis
  - Acute hyperthyroidism (likely secondary to thyroiditis)
  - Liver toxicity
  - Diffuse arthralgias

- Treatment is high doses of steroids. 2mg/kg/day or 160mg daily of IV methylprednisolone was started.
  - MRI of the brain revealed a normal-appearing pituitary gland.
  - Not treated with beta blockers or thioramides due to lack of thyrotoxic symptoms, though these medications were considered.
  - The patient tolerated high dose steroids and he was discharged on hospital day three on an oral steroid taper.
  - Recurrence of carcimona in the neck responded to ICP therapy and dramatically decreased in size.

Discussion

Hypophysitis
- irAEs occur in 60-85% of patients receiving Ipilimumab. 74 - 85% of patients receiving Nivolumab, and 95% of patients receiving combination therapy with 55% classified as severe
- Hypophysitis (a previously rare disorder) has emerged as distinctively related to CTLA4-blocking antibodies, notably Ipilimumab
- Incidence ranges between 5 - 16%
- Ectopic remains to be elucidated
- Symptoms are non-specific and can include fatigue, headache, vertigo, and subjective fevers/chills
- May progress to a life-threatening adrenal crisis including hypotension, electrolyte imbalance, and dehydration if it is not promptly recognized and treated with immunosuppression

Evaluation
- When hypophysitis is suspected, evaluation of pituitary function and brain MRI should be completed
- On MRI, pituitary gland is enlarged with thickening of the stalk in most cases
- MRI may be normal 20% of the time as seen in this case

Treatment
- 1-2mg/kg/day of prednisone equivalent is recommended for initial treatment
- If there is no improvement, further immunosuppression is indicated with the addition of mycophenolate, TNFα antagonists, or tacrolimus
- There is no evidence to show immunosuppression decreases anti-tumor effects of immunotherapy
- irAEs may in fact represent a positive response to treatment and additional trials of immunotherapy should be considered once toxicity resolves

Conclusions

This case exemplifies a cluster of the potential toxic side effects of immunotherapy medications, known as irAEs. This is a growing and under-recognized toxidrome. Presentations are diverse as any tissue can be effected, making diagnosis challenging. Most frequent irAEs involve the skin, bowel, endocrine organs, liver, and lungs. Hypophysitis is an irAE which has been definitively associated with Ipilimumab. Immunotherapy toxicity is distinct from chemotherapy toxicity in multiple respects. Most importantly, prompt recognition and rapid treatment with immunosuppression is essential to prevent potentially life-threatening complications.

References

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.

Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management.

Endocrine toxicity of cancer immunotherapy targeting immune checkpoints.

Endocrine side effects induced by immune checkpoint inhibitors.