Immunotherapy Toxicity Manifesting As Hypophysitis, Thyroiditis, and Liver Injury

David Grimaldi, MD

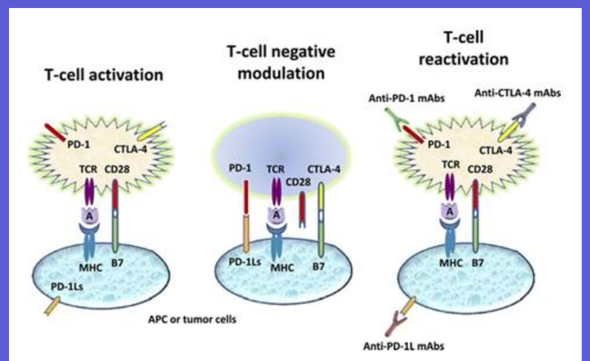
Internal Medicine Residency, Maine Medical Center, Portland, ME

Maine Medical Center
MaineHealth

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).

ICPi 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, myocarditis, renal injury, and hematologic toxicity. ICPis 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

HPI

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 supraclavicular lymph nodes
- Started on **Ipilimumab and Nivolumab** immunotherapy one month prior to this presentation to Maine Medical Center.

Additional home medications

Mitotane 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 lymphadenopathy or thyromegaly.
Cardiovascular: Regular rate and rhythm. No murmurs or rubs.
Chest: Clear to auscultation bilaterally.
Abdomen: Chronic surgical scars across chest and RUQ. Diffusely tender to palpation. Non-distended. Normoactive bowel sounds.
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	TSH: <0.02
BMP: normal	Free T4: >8
Calcium: 9.5	Prolactin: 22.3 (4.1 – 18.4)
APT: 104 (39 – 117)	FSH: 63.5 (1.5 – 12.4)
AST: 82 (0 – 40)	LH: 73.7 (1.7 – 8.3)
ALT: 186 (10 – 47)	Testosterone, total: 1,215 (250 – 1,100)
Bilirubin: 0.4	

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 thionamides 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 carcinoma in the neck responded to ICPi therapy and dramatically decreased in size.

References

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. J B A G Haanen, F Carbonnel, C Robert, K M Kerr, S Peters, J Larkin, K Jordan. Annals of Oncology 28, July 2017

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Discussion

Hypophysitis

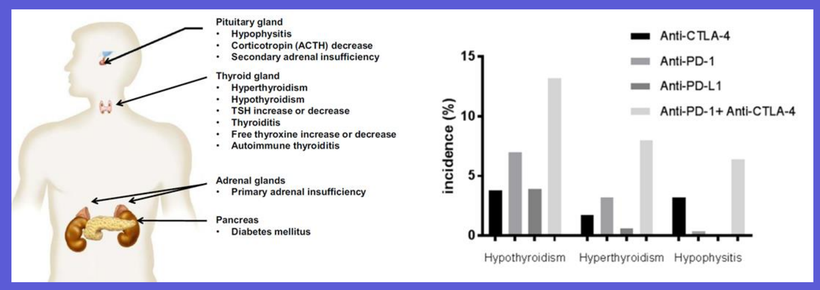
- irAEs occur in 60-85% of patients receiving Ipilimumab, 74 - 85% of patients receiving Nivolumab, and 95% of patients receiving combination therapy with 55% classified as severe
- Hypophysitis (a previously rare disorder) has emerged as distinctively related to CTLA4-blocking antibodies, notably Ipilimumab
  - Incidence ranges between 5 - 16%
- Etiology 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 **immunosuppresion**

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.