THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

“60 Year Old Woman On Immune Checkpoint Inhibitor With Hyperthyroidism”

Dr. Darji does not have any relevant financial relationships with any commercial interests.

ENDORAMA:
60 Year Old Woman On Immune Checkpoint Inhibitor With Hyperthyroidism

Monika Darji

October 25th, 2018

Objectives

- Review the endocrine related adverse effects associated with immune checkpoint inhibitors
- Discuss the range of thyroid dysfunction induced by immune checkpoint inhibitors
- Discuss the management of thyroid disorders associated with immune checkpoint inhibitors

Chief Complaint

60 year old Caucasian female presents with weight loss, tremors, and diarrhea

HPI

- Patient reports the following symptoms over the last 6 weeks:
  - 15 lb unintentional weight loss
  - Multiple episodes of diarrhea daily
  - Tremor involving both hands and arms
  - Heat intolerance
  - Palpitations
  - Muscle weakness
- Patient was directly admitted from Oncology clinic

Oncology History

- Patient was diagnosed with metastatic melanoma in 6/2018
  - pT3N1, stage IIIc disease per AJCC 8th ed
  - Lesion on the right side of neck s/p wide local excision
  - Irregular 3x2x2cm right parotid gland mass s/p parotidectomy, pathology positive for metastatic disease
  - Positive right cervical lymph node
  - Started adjuvant nivolumab in 7/2018 (received 3 doses)

Additional history

- ROS: Denies diaphoresis, anxiety. Denies neck masses or pain, voice changes, dysphagia, eye symptoms
- Past Medical History: type 2 diabetes, asthma
- Past Surgical History: neck lesion wide local excision, parotidectomy
- Family History: no family history of thyroid disease, father – colon cancer
- Social History: married with 3 kids, works in a factory, 45 pack year smoking history – quit in 2012. Denies alcohol and illicit drugs

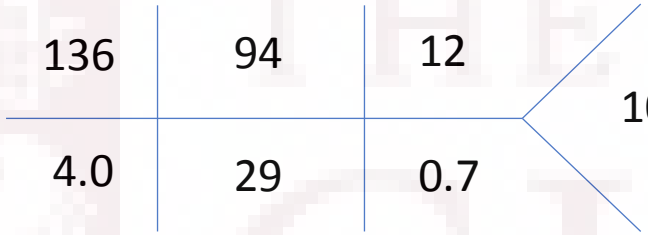
Additional history

- Meds: metformin, albuterol prn, zofran prn
- Allergies: NKDA

Physical Exam

- Vitals: 74 kg, BMI 26, Temp 98.6, **HR 110**, RR 17, BP 132/84, SpO2 100%
- Constitutional: no acute distress
- HEENT: EOMI, no exophthalmos, no lid lag
- Neck: supple, **diffuse thyromegaly**, no thyroid nodules
- Cardiovascular: **tachycardic**, regular rhythm
- Pulmonary/Chest: good respiratory effort, clear to auscultation bilaterally
- Abdomen: soft, non-tender, nondistended
- Extremities: no edema
- Neurological: alert, oriented, **4/5 muscle strength in all four extremities, tremor in bilateral upper extremities**
- Skin: warm, dry
- Psychiatric: not agitated

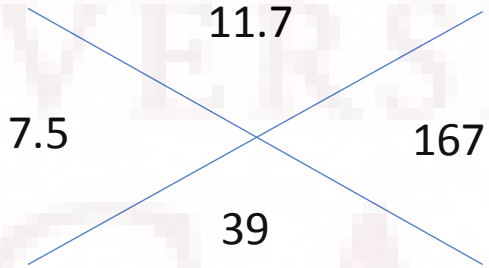
Admission Labs



Ca 9.1

108

Anion gap 13



Total protein	6.5	Alkaline phosphatase	0	TSH 0.01 (L)	Ref: 0.3-4.0
Albumin	3.4	ALT	19	Free T4 3.28 (H)	Ref: 0.9-1.7
Total bilirubin	0.3	AST	25	Total triiodothyronine 362	Ref: 80-195

TSI negative

Additional testing

- Patient had labs from 9/2018 completed in Oncology clinic

TSH 0.01 (L)	Ref: 0.3-4.0
Free T4 2.31 (H)	Ref: 0.9-1.7

- Thyroid ultrasound showed increased vascularity and no discrete nodules

Immune Checkpoint Inhibitors (ICI)

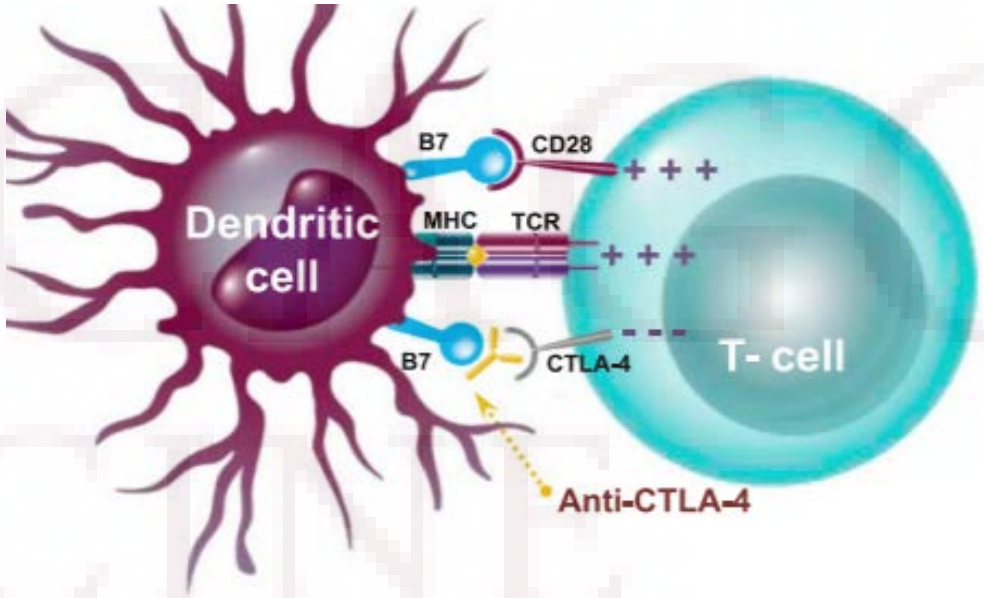
- Monoclonal antibodies that block immune inhibitory ligands CTLA-4 and PD-1
- First agent approved in 2011
- Have significantly improved the life expectancy of patients with certain malignancies
- Used in melanoma, lung cancer, renal cell carcinoma
- Additional drugs in development

How does it work?

- ICIs work by reversing the mechanisms that normally block immune responses to malignancy and in maintaining control of antitumor immunity
- ICIs block negative regulators (checkpoints) of T-cell activation and function

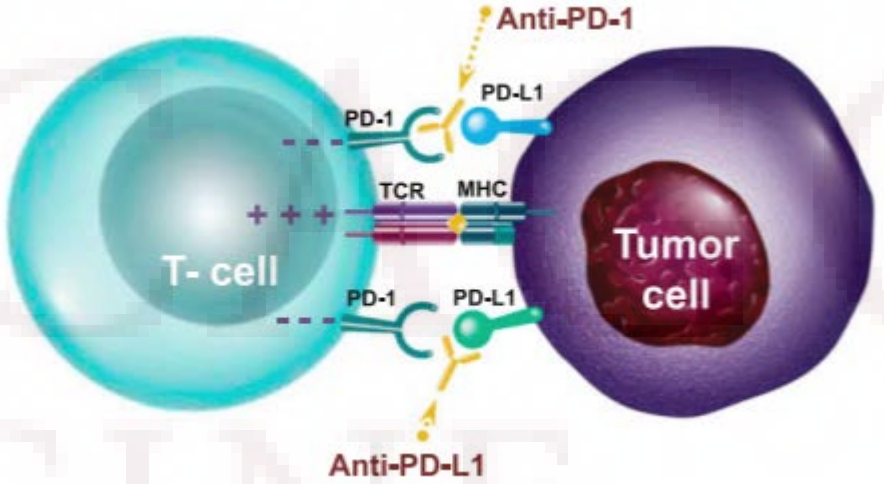
CTLA-4

- Present in lymph tissue
- CTLA-4 present in naïve T-cells and regulatory T-cells
- Binds to CD 80/86 on antigen presenting cells to inhibit immune response
- CTLA-4 inhibitors = ipilimumab and tremelimumab



PD-1 and PD-L1

- Present in peripheral tissues, PD-1 expressed on chronically activated T-cells. PD-L1 expressed on stromal cells, tumor cells, and antigen-presenting cells
- Binding -> inhibits immune response
- PD-1 inhibitors = nivolumab and pembrolizumab
- PD-L1 inhibitors = atezolizumab, avelumab, and durvalumab



ICI

Table 1. Checkpoint blockade drug classes and FDA-approved indications*

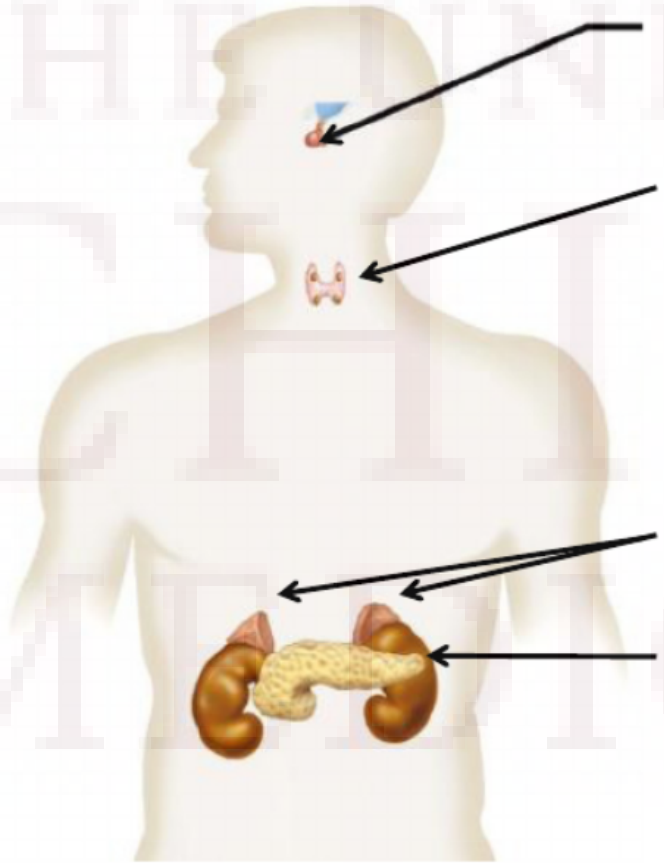
		Disease sites approved										
Drug class	Name	Melanoma	NSCLC	RCC	HL	Urothelial	HNSCC	Merkel	MSI-H CRC	Gastric	HCC	*MSI-H*
CTLA4 blockade	Ipilimumab	x										
	Tremelimumab											
PD1 blockade	Nivolumab	x	x	x	x	x	x		x		x	
	Pembrolizumab	x	x		x	x	x		x	x		x
PDL1 blockade	Atezolizumab		x			x						
	Durvalumab		x			x						
	Avelumab					x		x				

*CTLA4 = cytotoxic T-lymphocyte antigen 4; FDA = US Food and Drug Administration; HCC = hepatocellular carcinoma; HL = Hodgkin lymphoma; HNSCC = head and neck squamous cell carcinoma; MSI-H = microsatellite instability–high cancer, unresectable or metastatic; MSI-H CRC = microsatellite instability–high colorectal cancer NSCLC = non–small cell lung cancer; PD1 = programmed death 1; PDL1 = programmed death 1 ligand; RCC = renal cell carcinoma.

Immune related adverse events (irAE)

- Typical irAEs affect skin, GI tract, liver, and endocrine system
- Rare irAEs include uveitis, conjunctivitis, neuropathy, myopathy, pancreatitis, pneumonitis, cytopenias, and nephritis
- Endocrine irAEs often irreversible
  - Autoimmune thyroid disease, hypophysitis, adrenal insufficiency, type 1 diabetes

Endocrine irAEs



Pituitary gland
- Hypophysitis
- Corticotropin (ACTH) decrease
- Secondary adrenal insufficiency[a]

Thyroid gland
- Hyperthyroidism
- Hypothyroidism
- TSH increase or decrease
- Thyroiditis
- Free thyroxine increase or decrease
- Autoimmune thyroiditis

Adrenal glands
- Primary adrenal insufficiency[b]

Pancreas
- Diabetes mellitus

Incidence

- Barroso-Sousa et al. published a systematic review and meta-analysis that included 7551 patients in 38 randomized trials in JAMA Oncology 2018
- The overall incidence of endocrinopathies is approximately 10% of patients treated with ICIs
- Endocrine irAEs were significantly higher with combination therapy compared with monotherapy
- Among patients on monotherapy regimens
  - Incidence of thyroid dysfunction was higher in those treated with anti–PD-1 agents
  - Incidence of hypophysitis was highest in those treated with ipilimumab
- No association between the tumor type and the incidence of ICI-induced thyroid dysfunctions

Incidence

- The overall incidence of hypothyroidism estimated to be 6.6% (95% CI, 5.5%-7.8%)
- The overall incidence of hyperthyroidism estimated to be 2.9% (95%CI, 2.4%-3.7%)

All grade hypothyroidism			
Variable	Predicted Incidence, % (95% PI)	Odds ratio (95% CI)	*P* Value
ICI regimens			
CTLA-4	3.8 (1.9 - 7.8)	Reference	
PD-1	7.0 (3.9 - 12.3)	1.89 (1.17 - 3.05)	0.0089
PD-L1	3.9 (1.7 - 8.4)	1.01 (0.49 - 2.07)	0.9861
Combination*	13.2 (6.9 - 23.8)	3.81 (2.10 - 6.91)	<.0001
All grade hyperthyroidism			
Variable	Predicted Incidence, % (95% PI)	Odds ratio (95% CI)	*P* Value
ICI regimens			
CTLA-4	1.7 (0.8 - 3.8)	Reference	
PD-1	3.2 (1.7 - 5.7)	1.89 (1.02 - 3.52)	0.0438
PD-L1	0.6 (0.2 - 1.8)	0.35 (0.12 - 1.07)	0.0653
Combination*	8.0 (4.1 - 15.3)	5.07 (2.45 - 10.52)	<.0001
PD-1 agent			
Nivolumab	2.5 (1.3 - 4.6)	Reference	
Pembrolizumab	3.8 (2.1 - 6.9)	1.56 (1.01 - 2.39)	0.0428

* Combination = nivolumab plus ipilimumab

Incidence

eTable 3. Meta-regression model results for any grade hypophisitis in patients with melanoma

Class	Predicted Incidence, % (95% PI)	Odds ratio (95% CI)	*P* Value
ICI regimens			
CTLA-4	3.8 (2.7 - 5.2)	Reference	
PD-1	1.1 (0.8 - 1.6)	0.29 (0.18 - 0.49)	<.0001
Combination	8.0 (5.9 - 10.8)	2.24 (1.39 - 3.60)	0.0009

* Combination = nivolumab plus ipilimumab

The overall observed incidence of hypophysitis

- 6.4% with combination therapy
- 3.2% with CTLA-4 inhibitors
- 0.4% with PD-1 inhibitors
- <0.1% with PD-L1 inhibitors

Onset of endocrine irAEs

- For ipilimumab, the median time to onset of endocrine irAEs ranged from 7–20 weeks
  - Hypophysitis - Median time to onset of symptoms was 4 months
  - Hypothyroidism - Median time to onset of symptoms was 5 months
- For nivolumab, median time to onset of symptoms was:
  - Hypophysitis - 4.9 months (range: 1.4–11 months)
  - Adrenal insufficiency - 4.3 months (range: 15 days to 21 months)
  - Hypothyroidism or thyroiditis resulting in hypothyroidism - 2.9 months (range: 1 day to 16.6 months)
  - Hyperthyroidism - 1.5 months (range: 1 day to 14.2 months)
- For CTLA-4 inhibitors, studies have shown worsened toxicity with higher doses
- For PD-1 inhibitors, overall toxicity is similar across a wide dose range

Monitoring

- Baseline TSH and free T4 level should be checked before beginning treatment with ICI
  - Should be monitored at least monthly for the first six months
  - If no abnormalities during the first six months and the patient is asymptomatic, TSH and free T4 can be checked quarterly for months 6 to 12 and then every six months

Thyroid dysfunction

Table 2. Possible immunotherapy-induced changes in thyroid function based on laboratory values

TSH	Free T4	T3 total	Possible diagnoses
Low	Normal-high	Normal-high	Transient thyrotoxic phase of thyroiditis*
			Graves' disease (less common)
Low or normal	Low	Low	Secondary hypothyroidism due to hypophysitis/pituitary dysfunction†
High	Low-normal	Low-normal	Primary hypothyroidism/hypothyroid phase of thyroiditis*

*May evolve from a thyrotoxic phase to permanent hypothyroidism. TSH = thyroid-stimulating hormone.
†Thyroid hormone therapy should be instituted together with adrenal steroid replacement, unless adrenal insufficiency has been ruled out.

Hypothyroidism is the most common thyroid abnormality

Hypothyroidism

Grading	Management
G1: TSH <10 mIU/L and asymptomatic.	▪ Should continue ICPi with close follow-up and monitoring of TSH, FT4.
G2: Moderate symptoms; able to perform ADL; TSH persistently >10 mIU/L.	▪ May hold ICPi until symptoms resolve to baseline. ▪ Consider endocrine consultation. ▪ Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist >10 mIU/L (measured four weeks apart). ▪ Monitor TSH every six to eight weeks while titrating hormone replacement to normal TSH. ▪ FT4 can be used in the short term (two weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low. ▪ Once adequately treated, should monitor thyroid function (at least TSH) every six weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable.
G3 to 4: Severe symptoms; medically significant or life-threatening consequences; unable to perform ADL.	▪ Hold ICPi until symptoms resolve to baseline with appropriate supplementation. ▪ Endocrine consultation. ▪ May admit for IV therapy if signs of myxedema (bradycardia, hypothermia). ▪ Thyroid supplementation and reassessment as in G2.

American Society of Clinical Oncology Clinical Practice Guideline

Hyperthyroidism

Grading	Management
G1: Asymptomatic or mild symptoms.	▪ Can continue ICPi with close follow-up and monitoring of TSH, FT4 every two to three weeks until it is clear whether there will be persistent hyperthyroidism (refer below) or hypothyroidism (refer to 4.1.1).
G2: Moderate symptoms; able to perform ADL.	▪ Consider holding ICPi until symptoms return to baseline. ▪ Consider endocrine consultation. ▪ Beta-blocker (eg, atenolol, propranolol) for symptomatic relief. ▪ Hydration and supportive care. ▪ Corticosteroids are not usually required to shorten duration. ▪ For persistent hyperthyroidism (>6 weeks) or clinical suspicion, work-up for Graves' disease (TSI or TRAb) and consider thionamide (methimazole or PTU). ▪ Refer to endocrinology for Graves' disease.
G3 to 4: Severe symptoms; medically significant or life-threatening consequences; unable to perform ADL.	▪ Hold ICPi until symptoms resolve to baseline with appropriate therapy. ▪ Endocrine consultation. ▪ Beta-blocker (eg, atenolol, propranolol) for symptomatic relief. ▪ For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1 to 2 mg/kg/day or equivalent tapered over one to two weeks; consider also use of SSKI or thionamide (methimazole or PTU).

American Society of Clinical Oncology Clinical Practice Guideline

Hyperthyroidism

- Graves' disease is usually persistent and should be considered if hyperthyroidism lasts >5-6 weeks
- Ophthalmopathy and thyroid bruit are suggestive of Graves' disease
- The thyrotoxic phase of thyroiditis is the most common cause of hyperthyroidism in patients treated with ICI
  - Usually resolves within a 2-4 weeks to normal or hypothyroidism
  - Should be monitored closely for progression to hypothyroidism, with labs at least every 2-3 weeks
  - Symptomatic management with a beta-blocker can be used

Iyer et al.

THYROID
Volume 28, Number 10, 2018

DOI: 10.1089/thy.2018.0116

ORIGINAL STUDIES

THYROID FUNCTION AND DYSFUNCTION

Immune-Related Thyroiditis with Immune Checkpoint Inhibitors

Priyanka C. Iyer,[1,2] Maria E. Cabanillas,[1] Steven G. Waguespack,[1] Mimi I. Hu,[1] Sonali Thosani,[1] Victor R. Lavis,[1] Naifa L. Busaidy,[1] Sumit K. Subudhi,[3] Adi Diab,[4] and Ramona Dadu[1]

Iyer et al.

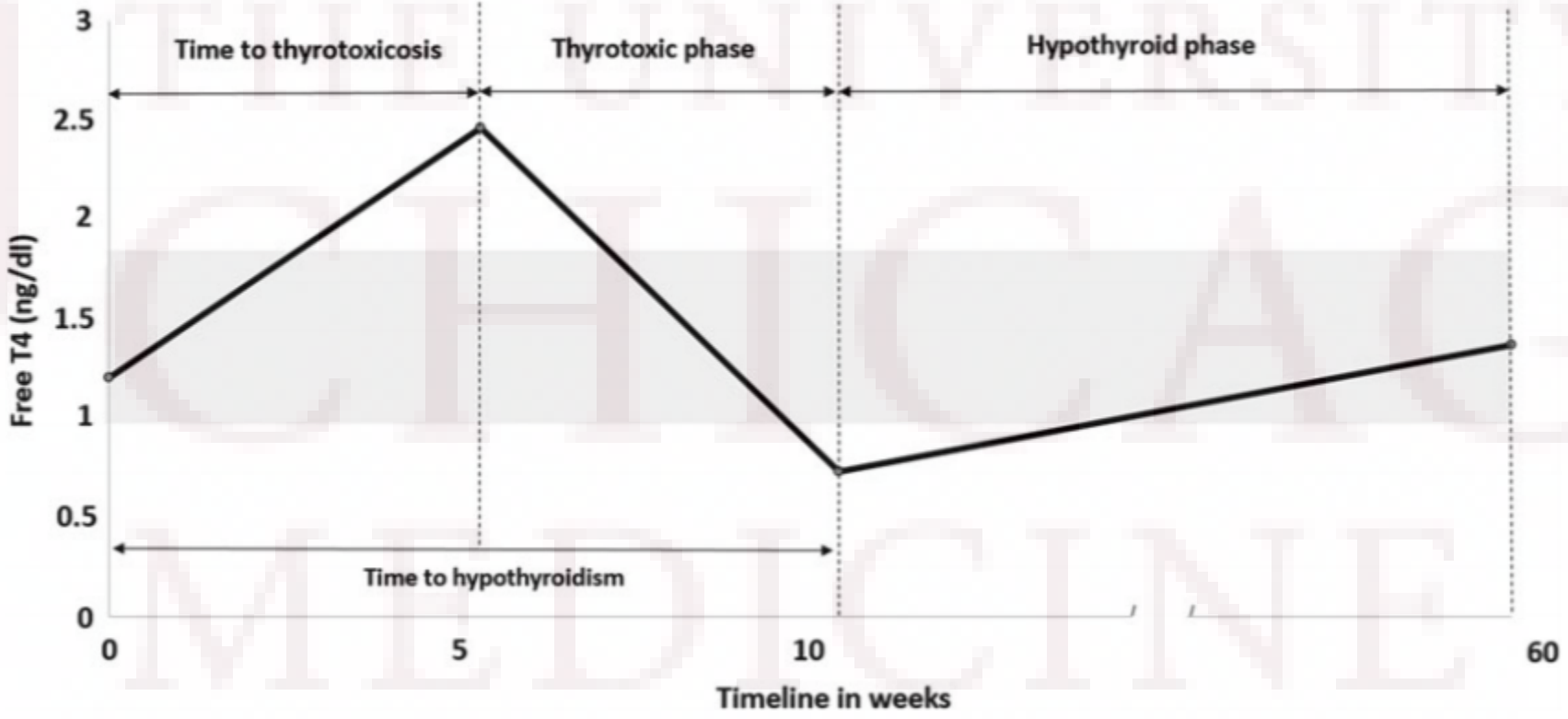
- 657 patients treated with ICI during study period
  - Patients with preexisting thyroid disease, hypothyroidism without thyrotoxic phase, hyperthyroidism 2/2 Graves' diseases or toxic nodule were excluded
- 43 patients met inclusion criteria

TABLE 1. BASELINE CHARACTERISTICS

Patient characteristics	n = *43*
Age (years) at treatment start, median (range)	57 (21–81)
Sex, *n* (%)	
Male	22 (51)
Female	21 (49)
Ethnicity, *n* (%)	
Caucasian	36 (84)
Black	3 (6)
Hispanic	2 (5)
Asian	2 (5)
Type of cancer, *n* (%)	
Melanoma	10 (23)
Renal-cell carcinoma	9 (21)
Lung cancer	8 (19)
Urothelial carcinoma	5 (12)
Colon cancer	4 (9)
Glioblastoma multiforme	3 (7)
Ovarian cancer	2 (4.5)
Others[a]	2 (4.5)
Type of immunotherapy, *n* (%)	
Ipilimumab + nivolumab	17 (39.5)
Nivolumab	14 (32.5)
Pembrolizumab	9 (21)
Durvalumab + tremelimumab	2 (4.65)
Tremelimumab	1 (2.35)
Follow-up time (months), median (range)	17.63 (1–41.25)

[a]Other cancer diagnoses included pancreatic adenocarcinoma in one patient and non-Hodgkin's lymphoma in one patient.

Iyer et al.


Time to thyrotoxicosis
Thyrotoxic phase
Hypothyroid phase
Free T4 (ng/dl)
3
2.5
2
1.5
1
0.5
0
Time to hypothyroidism
0
5
10
60
Timeline in weeks

Iyer et. al

- 14/43 patients (33%) were symptomatic in thyrotoxic phase
- 37/43 (84%) developed hypothyroidism requiring levothyroxine treatment
- 4/43 (9%) patients recovered from transient hypothyroidism without levothyroxine
  - All 4 of these patients received steroids for other reasons (for chemotherapy or other irAEs)
- 2/43 patients died before they could develop hypothyroidism
- 5/37 (12%) patients were symptomatic during the hypothyroid phase

Iyer et. al

TABLE 2. EFFECT OF STEROID EXPOSURE AND ELEVATED THYROID ANTIBODIES ON LEVOTHYROXINE DOSE

Antibody and steroid exposure versus dose	*<1 μg/kg (n/10)*	*1–1.6 μg/kg (n/17)*	*>1.6 μg/kg (n/9)*
Ab+/steroid+, (*n*)	1	4	0
Ab+/steroid–, (*n*)	1	4	4
Ab–/steroid+, (*n*)	6	3	2
Ab–/steroid–, (*n*)	2	3	1

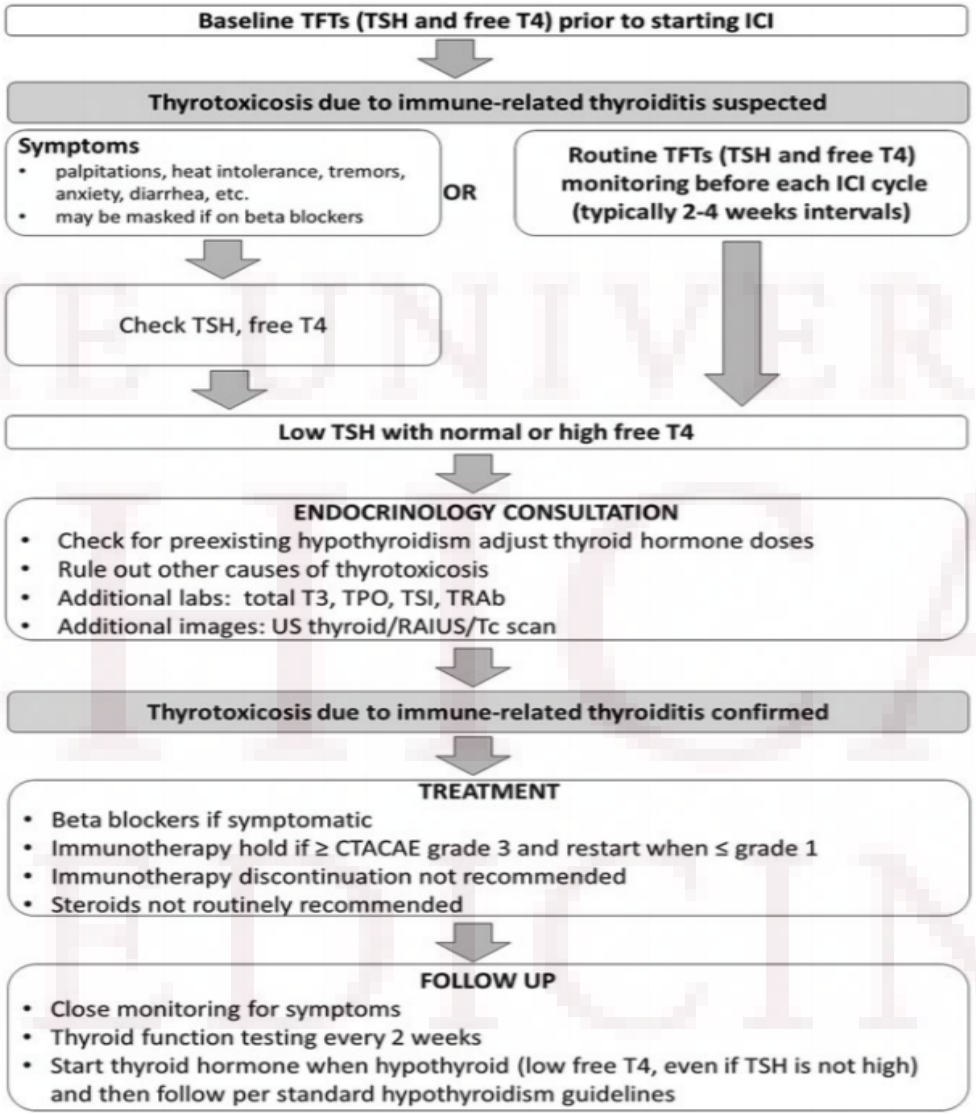
TABLE 3. TIMELINE OF THYROIDITIS DEPENDING ON INDIVIDUAL DRUG REGIMEN

Timeline (weeks)	*Pembrolizumab* (n = *9*)	*Nivolumab* (n = *14*)	*Ipilimumab + nivolumab* (n = *17*)	p
Time to thyrotoxicosis	5 [3.15–6.84]	6 [3.58–8.41]	2 [1.19–2.8]	0.423
Thyrotoxicosis phase	5 [3.61–6.38]	10 [8.18–11.81]	6 [4.07–7.92]	0.05
Time to hypothyroidism	10 [8.61–11.38]	17 [8.82–25.18]	10 [8.11–11.90]	0.09

Data shown are median [confidence interval].

Iyer et al.

- Thyroiditis related to ICI seems to be more commonly associated with anti-PD1 drugs used alone or in combination with anti-CTLA-4 agents
- Onset of hypothyroidism was significantly more rapid in patients treated with combined ipilimumab and nivolumab (10 weeks) than with nivolumab alone (17 weeks)
- Patients in this study were followed for 14 months, all the patients started on levothyroxine remained on this with normal TFTs at their last follow-up


Baseline TFTs (TSH and free T4) prior to starting ICI
Thyrotoxicosis due to immune-related thyroiditis suspected
Symptoms
palpitations, heat intolerance, tremors, anxiety, diarrhea, etc.
may be masked if on beta blockers
OR
Routine TFTs (TSH and free T4) monitoring before each ICI cycle (typically 2-4 weeks intervals)
Check TSH, free T4
Low TSH with normal or high free T4
ENDOCRINOLOGY CONSULTATION
Check for preexisting hypothyroidism adjust thyroid hormone doses
Rule out other causes of thyrotoxicosis
Additional labs: total T3, TPO, TSI, TRAb
Additional images: US thyroid/RAIUS/Tc scan
Thyrotoxicosis due to immune-related thyroiditis confirmed
TREATMENT
Beta blockers if symptomatic
Immunotherapy hold if ≥ CTACAE grade 3 and restart when ≤ grade 1
Immunotherapy discontinuation not recommended
Steroids not routinely recommended
FOLLOW UP
Close monitoring for symptoms
Thyroid function testing every 2 weeks
Start thyroid hormone when hypothyroid (low free T4, even if TSH is not high) and then follow per standard hypothyroidism guidelines

Back to our patient

- Our patient had persistent hyperthyroidism after 5-6 weeks so patient was started on methimazole 30mg daily and propranolol 20mg Q8H with improvement in symptoms
- Patient is scheduled for Endocrinology clinic follow up
- Per Oncology, nivolumab is being held for now

Objectives

- Review the endocrine related adverse effects associated with immune checkpoint inhibitors
- Discuss the range of thyroid dysfunction induced by immune checkpoint inhibitors
- Discuss the management of thyroid disorders associated with immune checkpoint inhibitors

References

- Uptodate, Patient selection criteria and toxicities associated with checkpoint inhibitor immunotherapy
- Barroso-Sousa, R. et al., Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens. JAMA Oncol. 2018;4(2):173-182
- Stamatouli, A.M. et al., Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors. Diabetes 2018;67:1471–1480.
- Fejzo, M.S., et al., Genetic analysis of hyperemesis gravidarum reveals associationwith intracellular calcium release channel (RYR2). Molecular and Cellular Endocrinology 2016.
- Brahmer, J.R. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology 2018.
- Ntali, G. Endocrine sequelae of immune checkpoint inhibitors. Hormones 2017, 16(4):341-350
- Girotra, M. The Current Understanding of the Endocrine Effects From Immune Checkpoint Inhibitors and Recommendations for Management. JNCI Cancer Spectrum (2018) 2(3)
- Sznol, M. Endocrine-related adverse events associated with immune checkpointblockade and expert insights on their management. Cancer Treatment Reviews 58 (2017) 70–76.
- Ferrari, S. M. Thyroid disorders induced by checkpoint inhibitors. Endocrine and Metabolic Disorders 2018.
- Iyer, P. Immune-Related Thyroiditis with Immune Checkpoint Inhibitors. Thyroid 2018