Immune Checkpoint Inhibitors (ICI) and Its Effect in the Endocrine System

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1

Disclosure

Consultant: Corcept Therapeutics, Moderna, Novo Nordisk, Recordarti

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Speakers Bureau: Amhryt; Ascendis; Moderna; Recordarti

Other: CDC/CMSS Grant, Veteran's Administration Grant, Primary Hyperaldosteronism Guidelines Endocrine Society; TF Member; Chair; AACE Oversight Guidelines Committee and Board of Director; Chair, Special Interest Group, Pituitary and Adrenal, ACP Board of Regents; EFF Board of Director

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Outline

Case 1

Drugs causing endocrine abnormalities

Cancer therapies and endocrine dysfunction (toxicities)

Immune checkpoint inhibitors

Case 2

Take home points

3

Case 1

55 y-o F presented to the ED with **4-day history of generalized malaise, fatigue and severe headache.**

Patient was recently dx with right leg **metastatic melanoma** s/p surgical mass excision of right leg.

SoHx and FHx: unremarkable

2 months prior to the admission patient was started on ipilimumab/nivolumab therapy

ROS

Gen: +fatigue, +12lb weight gain in 6 weeks

HEENT: + light headedness and dizziness

Abd: +nausea, denies V/D/C. + decreased appetite, no abdominal pain

Neuro: +HA

Skin: no new rashes or skin changes; + hair loss

Endo: + intermittent heat/cold intolerance

4

Case

Physical Exam:

VS: HR 88 BP 98/70 RR 19 SPo2 98% Wt 96kg BMI 32.23

GEN: uncomfortable, upright in chair with numerous blankets, A+O x3

HEENT: Dry oral mucosal, No lid lag/proptosis/stare, visual fields intact

NECK: thyroid non-tender, not enlarged

ABD:. Abd soft, nontender, no rigidity or guarding.

Skin: Flushed skin of upper chest extending to neck

Initial Labs

130	**97**	**19**	**70**
3.8	**26**	**1.24**	

CBC and LFTs WNL

WHAT ARE YOUR SUSPICIOUS?

WHAT TO DO NEXT?

5

Case

	Start therapy	4 weeks	6 weeks	Admission
TSH	2.235	0.030 (L)	7.514 (H)	18.061 (H)
Total T3		171		
Free T4		1.83 (H)	0.42 (L)	0.23 (L)

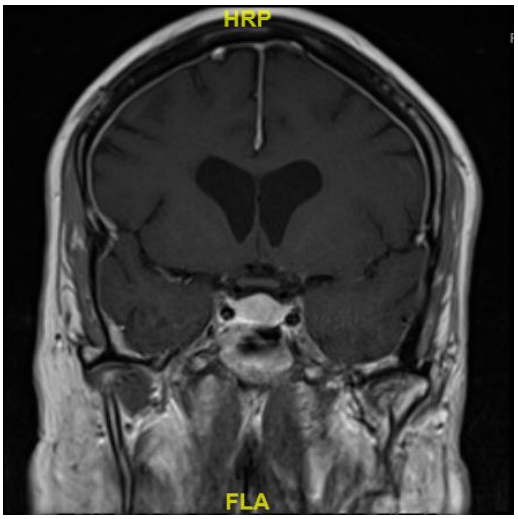
	AM cortisol	Plasma cortisol	ACTH
7 am	0.8 (LL)		
3:33PM		1.4	<5
4:03PM		16.4	
4:33PM		21.3	

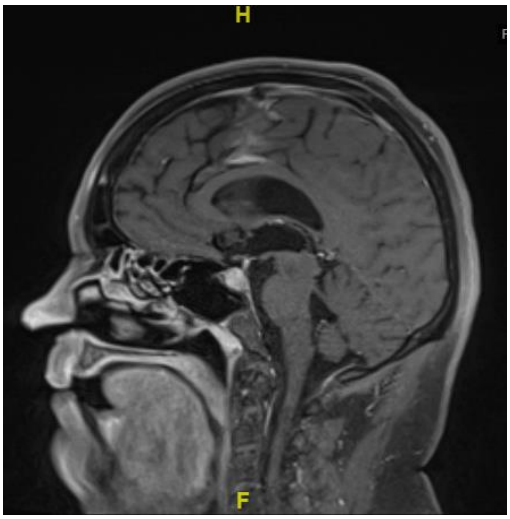
WHAT NEXT?

6

Case

MRI w/wo Contrast:





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Management and Follow up

Low AM cortisol w/ low ACTH level (normal stim) and characteristic findings of pituitary hypophysitis→ secondary adrenal insufficiency was diagnosed.

Patient was started on physiologic HC

TFTs suggested transient thyroiditis with progression to hypothyroidism. weight based levothyroxine (1.2mcg/kg) after receiving steroids was started

Had STIM TEST 6 months later, failed (as expected as corticotroph axis permanently affected in large number of patients with immune mediated hypophysitis)

Continues receiving immunotherapy infusions

8

What Other Condition the Patient Can Develop?

A. Hypercalcemia
B. Myocarditis
C. Myasthenia Gravis
D. Peripheral Ulcerative Keratitis
E. Lipodystrophy
F. Transient Cushing Syndrome
G. None of the Above
H. I don't know
I. All of the Above

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What Other Condition the Patient Can Develop?

Hypercalcemia

Myocarditis

Myasthenia Gravis

Peripheral Ulcerative Keratitis

Lipodystrophy

Transient Cushing Syndrome

None of the Above

I don't know

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- Sato K, Mano T, Iwata A, Toda T. Neurological and related adverse events in immune checkpoint inhibitors: a pharmacovigilance study from the Japanese Adverse Drug Event Report database. J Neurooncol. 2019 Aug 26
- Antoun J, Titah C, Cochereau I. Ocular and orbital side-effects of checkpoint inhibitors: a review article. Curr Opin Oncol. 2016 Jul;28(4):288-94
- Jehl A;Cugnet-Anceau C;Vigouroux C, et al. Acquired Generalized Lipodystrophy: A New Cause of Anti-PD-1 Immune-Related Diabetes.. Diabetes Care ; 2019/08/23

10

General

Drugs cause Endocrine abnormalities via

direct alteration of hormone production

changes in the regulation of the feedback axis and on hormonal transport

binding and signaling

interference with the hormonal assays (erroneous lab)

11

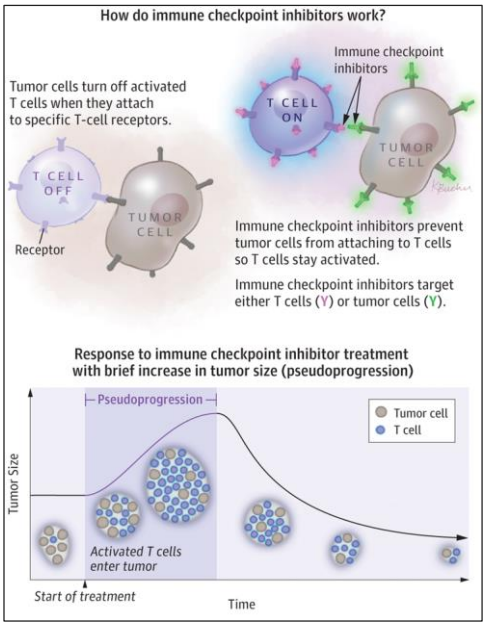
	Immune checkpoint inhibitors	Opioids	Psychotropics	Antiepileptic drugs	Glucocorticoids	Anabolic androgenic steroids	Oral contraceptives	Aromatase inhibitors	Androgen deprivation therapy	Antihypertensives	Cytotoxic agents
Drug-induced pituitary dysfunction	+	+				+					
Drug-induced SIADH	+	+	+	+							+
Drug-induced hyperprolactinemia		+	+				+			+ (verapamil, methyldopa)	
Drug-induced thyroid abnormalities	+		+	+						+ (beta-blockers)	+
Drug-induced calcium and vitamin D deregulation	+		+	+	+					+ (thiazides)	+
Drug-induced osteoporosis		+	+	+	+			+	+	+ (loop diuretics)	+
Drug-induced obesity			+	+	+			+	+		
Drug-induced diabetes	+		+	+	+			+	+	+ (calcium channel blockers, diazoxide, donidine)	+
Drug-induced dyslipidemia			+		+	+	+	+	+		+
Drug-induced adrenal dysfunction	+	+			+						+
Drug-induced pheo crisis		+	+		+					+ (beta-blockers)	
Drug-induced amenorrhea	+	+	+	+	+	+		+		+ (spironolactone)	+
Drug-induced hyperandrogenemia				+	+	+					
Drug-induced PCOS			+	+		+					
Drug-induced male infertility and sperm abnormalities	+	+	+	+	+	+			+	+ (beta-blockers, spironolactone)	+

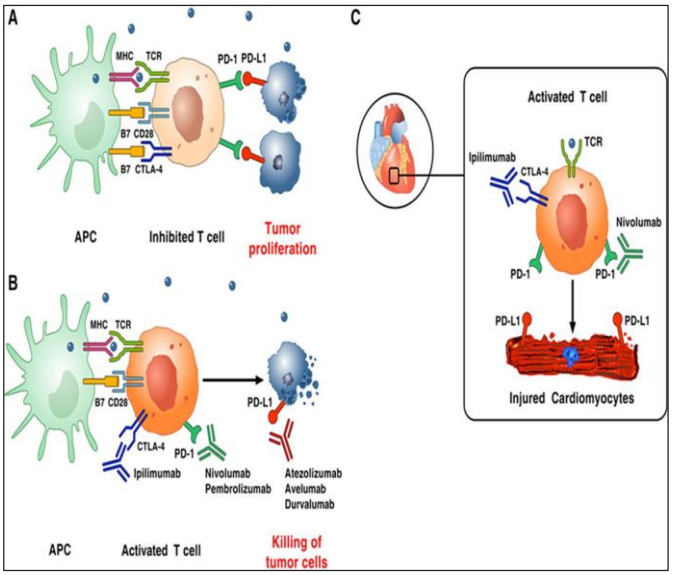
12

Immune Checkpoint Inhibitor

13

Checkpoint Inhibitors: MoA and Pathophysiology





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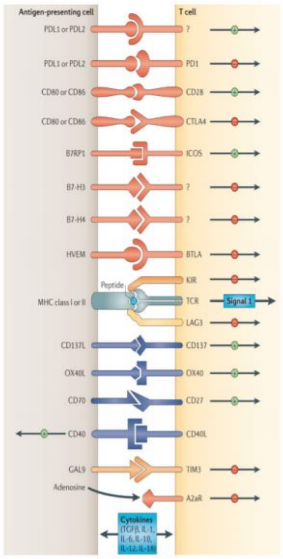
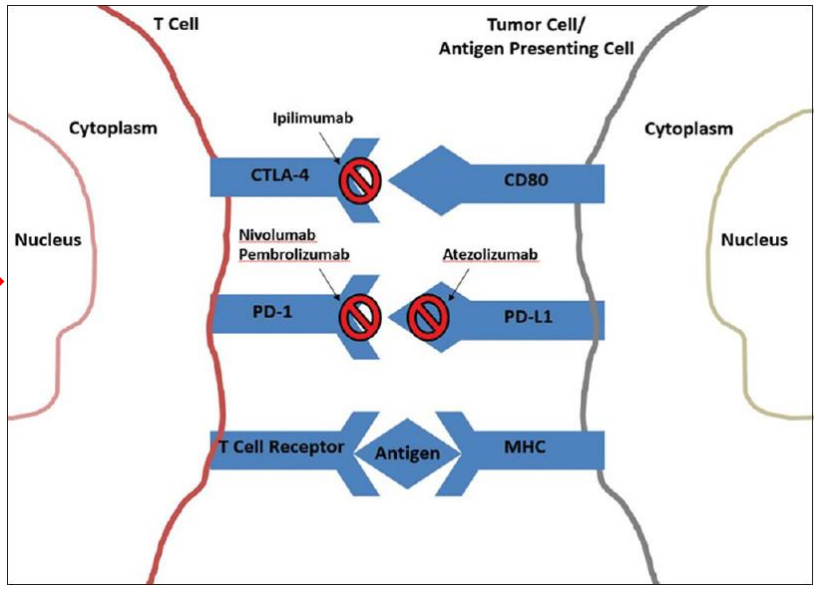
Circulation. 2017;136:1989-1992
Originally published November 20, 2017

14

Checkpoint Inhibitors: MoA and Pathophysiology





15

Immune Checkpoint Inhibitors (ICIs)

1996

Prof. James P. Allison

Nobel Prize of Medicine and Physiology 2018

Enhancement of Antitumor Immunity by CTLA-4 Blockade

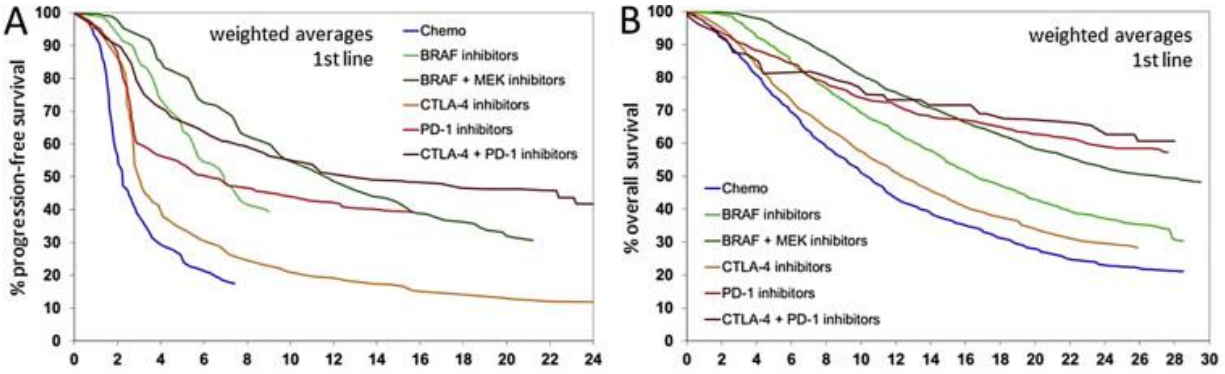
Dana R. Leach, Matthew F. Krummel, James P. Allison*

Off Label use in endocrine (case Reports)
-Aggressive pituitary Carcinomas
-ACC

Immune check point inhibitors	FDA approval	Cancer type
Anti-CTLA4		
Ipilimumab (Yervoy, Bristol–Myers Squibb)	2011	Advanced, metastatic melanoma
Anti-PD-1		
Pembrolizumab (Keytruda, Merck)	2014	Advanced melanoma Non-small cell lung cancer (NSCLC)—first line treatment in some patients Hodgkin's lymphoma Head and neck squamous cell carcinoma Advanced urothelial (bladder) cancer Advanced gastric cancer Any cancer with specific genetic features (microsatellite instability-high cancer)
Nivolumab (Opdivo, Bristol–Myers Squibb)	2014	Advanced melanoma Advanced NSCLC Advanced renal cell (kidney) cancer Urothelial (bladder) cancer Hodgkin's lymphoma Head and neck squamous cell carcinoma Colorectal cancer Hepatocellular (liver) cancer
Ipilimumab plus nivolumab	2015	BRAF WT advanced melanoma
Anti-PD-1L		
Atezolizumab (Tecentriq, Genentech)	2016	Certain types of advanced NSCLC Advanced urothelial (bladder) cancer
Durvalumab (Imfinzi, AstraZeneca)	2017	Metastatic urothelial (bladder) cancer
Avelumab (Bavencio, EMD Serono)		Merkel cell carcinoma Urothelial (bladder) cancer

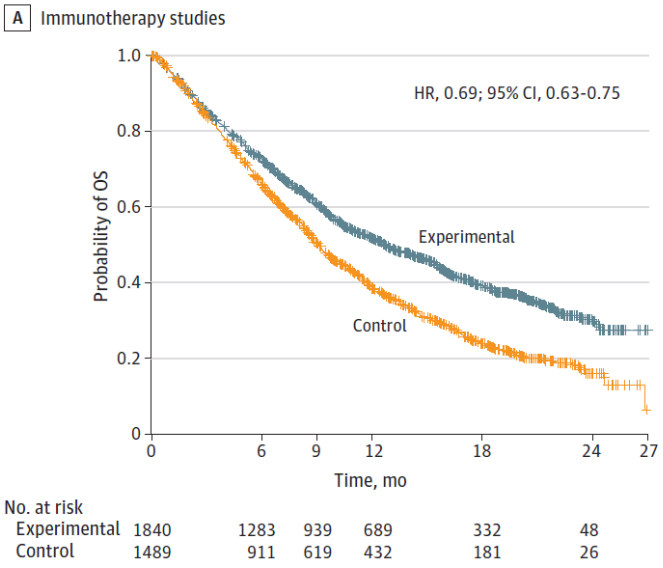
16

ICI and Melanoma Survival Rate



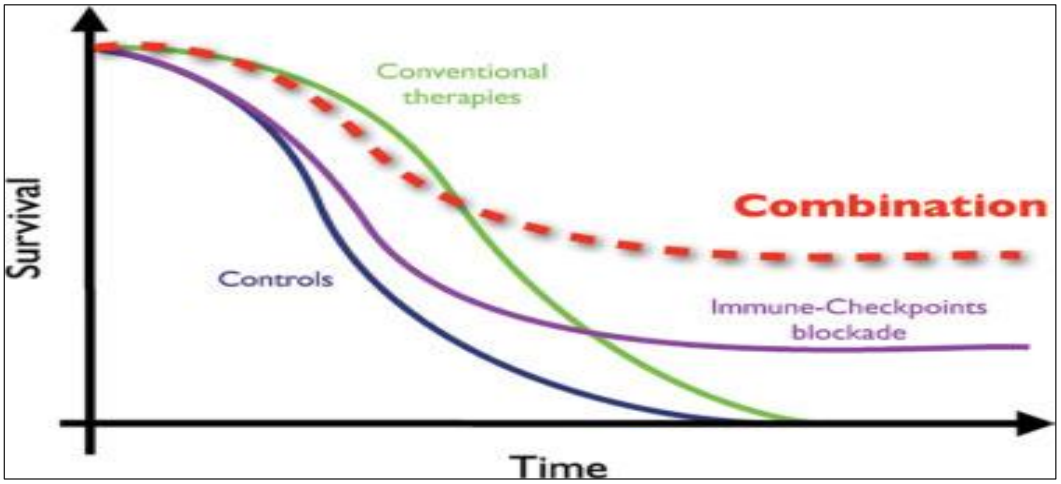
17

Survival in Metastatic NSCLC - OS



18

Benefit of Combined ICI



19

Checkpoint Inhibitors: Pathophysiology

- **Studies show that since CTLA-4 and PD-1 regulate distinct inhibitory pathways and have non-overlapping MoA, combination therapy with both is more efficacious than single therapy**

Everything comes with a cost...

- **By using these new drugs to aid the immune system to control neoplastic cells, immunologic tolerance can be altered and a higher risk for reactions mediated by self-directed antigens can be incurred.**

Sharma, et al. Science 03 Apr 2015:
Vol. 348, Issue 6230, pp. 56-61

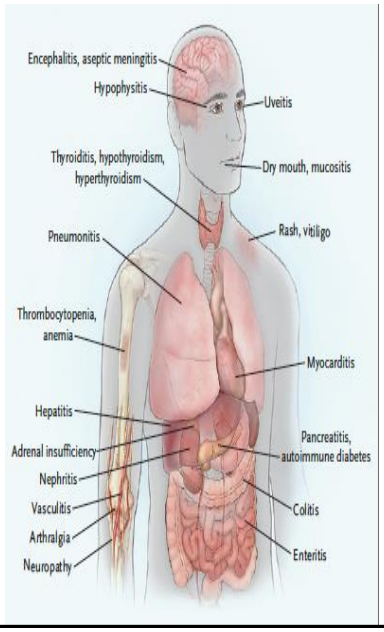
20

Immune Related Adverse Events (irAE)

Incidence 15-90%

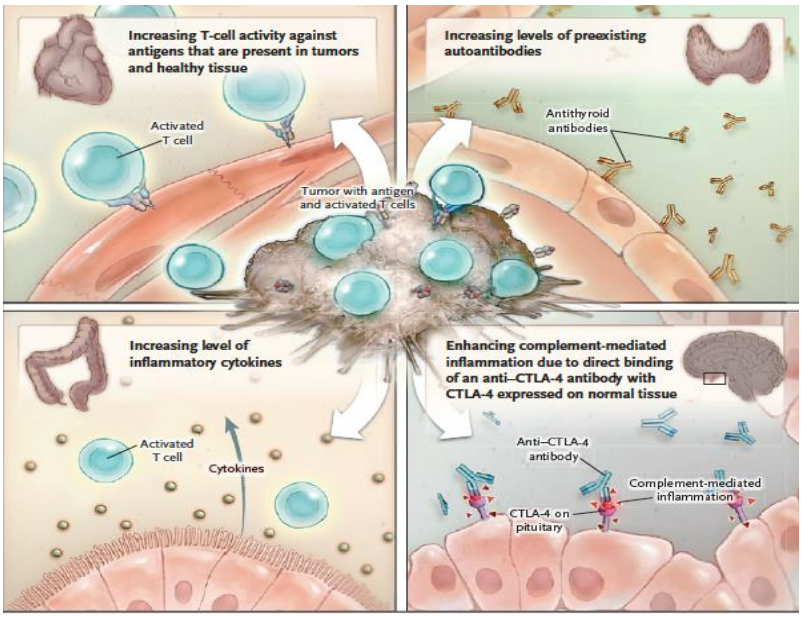
21

Immune Related Adverse Events (irAE)



22

Immune Related Adverse Events (irAE)



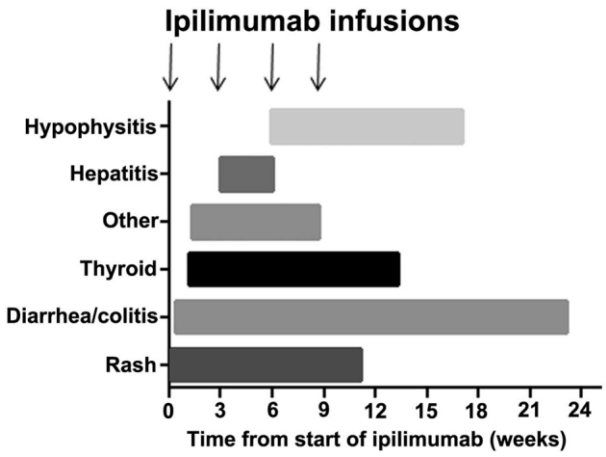
23

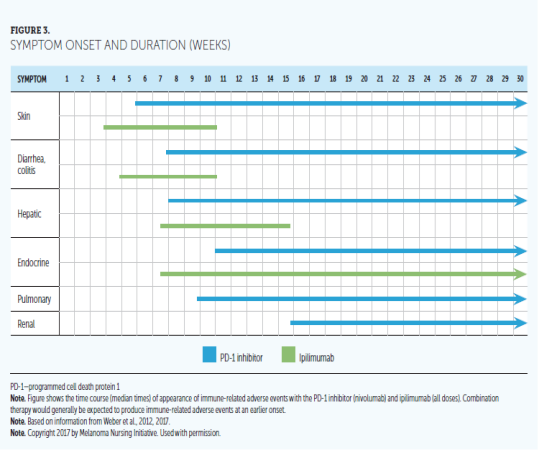
irAEs: Mechanism of Action

- IrAEs occur secondary to the enhanced immune-response that the drugs elicit, and can occur in any organ system
- It is important for physicians to be aware that irAEs can occur at any time–from the outset of treatment, during treatment, or after treatment has been discontinued
- Symptoms of endocrine related irAEs tend to be nonspecific but can be life threatening (more on this later)
- Unlike irAEs in other organ systems which generally resolve completely after appropriate therapy is administered, endocrine irAEs most often require permanent hormone replacement therapy
- Timing is also unpredictable. A pooled study of nivolumab monotherapy found that, although 85% of irAEs began within the first 16 weeks of therapy, they can occur more than a year after initiating treatment

24

irAE- Dose Dependent?





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CJON 2017, 21(4), 30-41 DOI: 10.1188/17.CJON.S4.30-41

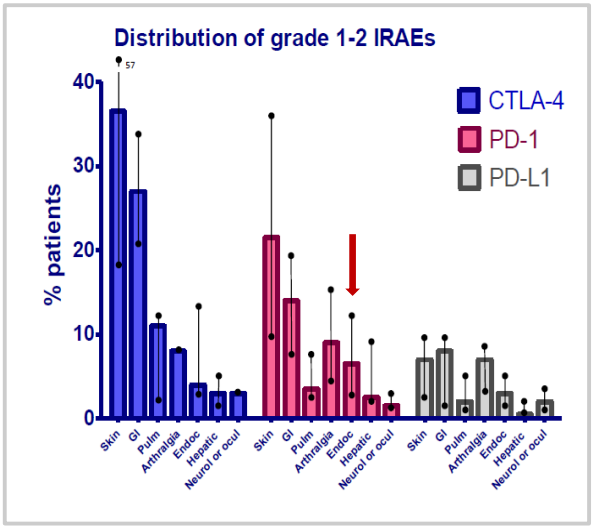
25

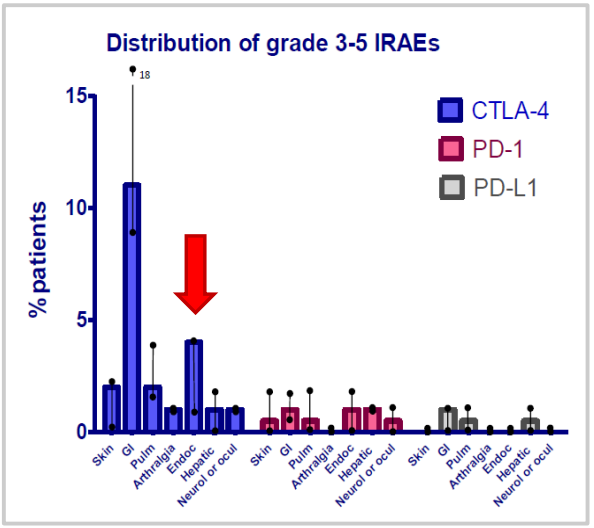
Common Terminology Criteria for Adverse Events (CTCAE)

Grade	Severity of AE (chemo and immune therapy)
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
3	Severe or medically significant but not immediately life-threatening; disabling; limiting self care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

26

Distribution of irAE by Grades

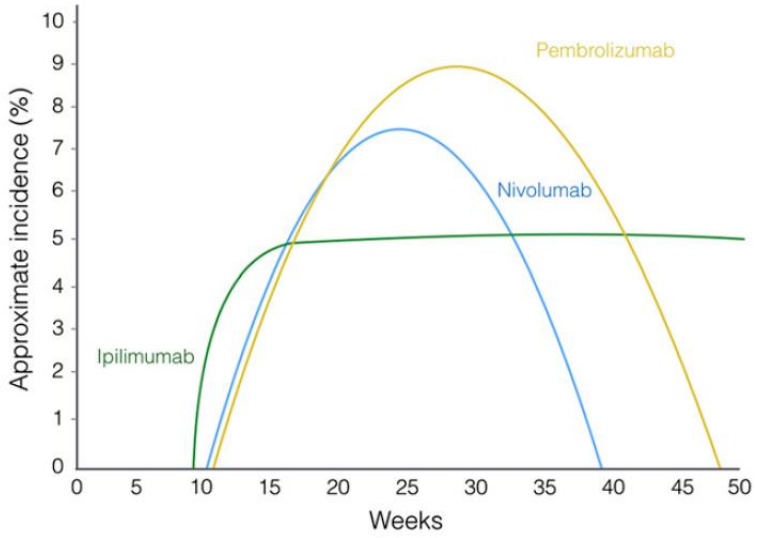




Michot JM et al. Eur J Cancer. 2016;54:139-48.

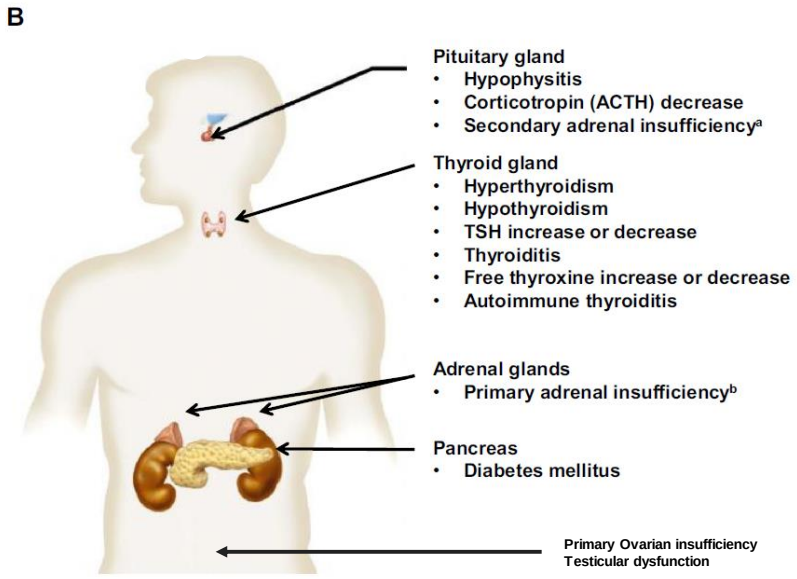
27

Timing of Endocrine irAE



28

Endocrine irAE



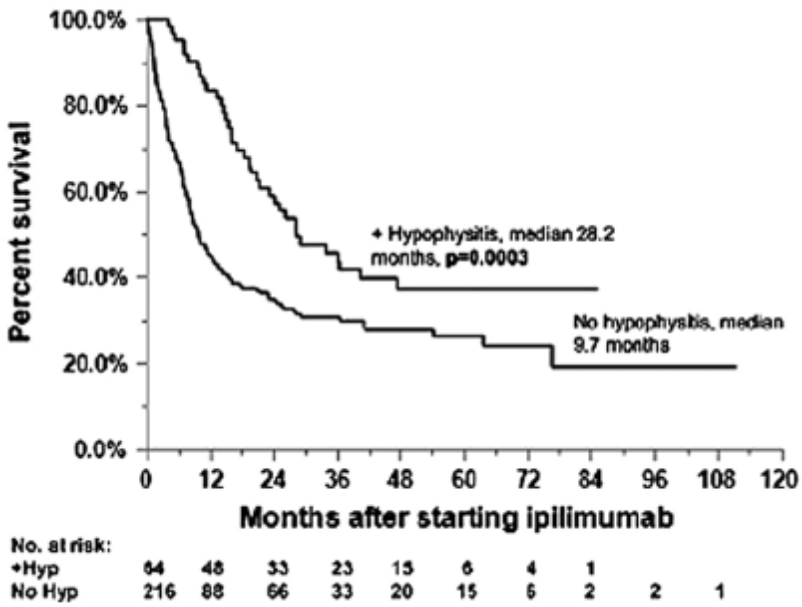
Thyroid more frequent (50%)

If TSH is high prior higher risk

29

		CTLA-4 inhibitor	PD-1/PD-L1 inhibitor
Pituitary	Hypophysitis/hypopituitarism	+++	–
	Isolated ACTH deficiency	+	++
Thyroid	Thyroiditis/transient hyperthyroidism	++	+++
	Hypothyroidism	++	+++
	Graves' disease/thyroid eye disease	+	?
Pancreas	Insulin-deficient diabetes	–	++
Adrenal	Primary adrenal insufficiency	+	+

30



31

Endocrinopathies

Need replacement

32

▸ **Table 1** Summary estimated incidence of endocrine adverse events on immune checkpoint inhibitors.

			Hypothyroidism		Hyperthyroidism		Thyroiditis		Hypophysitis		PAI		DM	
		Total patients	Analyzed patients	Summary incidence	Analyzed patients	Summary incidence	Analyzed patients	Summary incidence	Analyzed patients	Summary incidence	Analyzed patients	Summary incidence	Analyzed patients	Summary incidence
Target	Treatment	n	n (%)	% (95% CI)	n (%)	% (95% CI)	n (%)	% (95% CI)	n (%)	% (95% CI)	n (%)	% (95% CI)	n (%)	% (95% CI)
CTLA-4	Ipilimumab	4430	3614 (82%)	3.8 (2.6–5.5)	2147 (48%)	1.4 (0.8–2.4)*	1708 (39%)	2.1 (1.1–4.1)	3534 (80%)	5.6 (3.9–8.1)	1690 (38%)	1.4 (0.9–2.2)	NR	NR
	Tremelimumab	1171	N/A	up to 5.2%†	N/A	up to 5.2%†	N/A	up to 5.2%†	1037 (89%)	1.8 (1.1–2.9)	705 (60%)	1.3 (0.7–2.4)	NR	NR
PD-1	Nivolumab	3317	3317 (100%)	8.0 (6.4–9.8)	1710 (52%)	2.8 (2.1–3.8)	650 (20%)	1.6 (0.2–10.2)	1103 (33%)	0.5 (0.2–1.2)	979 (30%)	2.0 (0.9–4.3)*	619 (19%)	2.0 (0.7–5.8)*
	Pembrolizumab	4485	4461 (99%)	8.5 (7.5–9.7)*	3757 (84%)	3.7 (2.8–4.7)*	1916 (43%)	2.3 (1.2–4.6)	1381 (31%)	1.1 (0.5–2.6)	1691 (38%)	0.8 (0.3–2.0)*	941 (21%)	0.4 (0.2–1.3)
PD-L1	Atezolizumab	998	998 (100%)	6.0 (4.2–8.4)*	NR	NR	NR	NR	NR	NR	NR	NR	70 (7%)	1.4 (0.2–9.4)
	Avelumab	316	316 (100%)	5.5 (3.5–8.7)	88 (28%)	2.3 (0.6–8.6)	NR	NR	NR	NR	184 (58%)	1.1 (0.3–4.2)	88 (28%)	1.1 (0.2–7.6)
	Durvalumab	191	191 (100%)	4.7 (2.5–8.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Combined	Ipilimumab + Nivolumab	816	739 (91%)	16.4 (11.7–22.5)	520 (64%)	9.4 (7.1–12.3)	147 (18%)	3.8 (1.4–9.4)*	524 (64%)	8.8 (6.2–12.4)*	339 (42%)	5.2 (2.9–9.2)*	NR	NR
	Ipilimumab + Pembrolizumab	163	163 (100%)	15.1 (10.6–21.8)	163 (100%)	10.4 (6.6–16.1)	153 (94%)	4.6 (2.2–9.3)	153 (94%)	10.5 (6.5–16.4)	163 (100%)	7.6 (1.2–36.8)	153 (94%)	2.0 (0.6–5.9)
	Durvalumab + Tremelimumab	99	99 (100%)	10.2 (5.6–17.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

de Filette J et al. ErAE and Checkpoint Inhibitors … Horm Metab Res 2019; 51: 145–156

33

Hypophysitis

- **Incidence**

  0-17%* with Ipilimumab use, 0-5% tremelimumab, 23% with combination ipilimumab / nivolumab, 0.5-2% Nivolumab or prembrolizumab

  More common in male and older age (different from LAH)

  Affected axis: ACTH, TSH, Gonadal axis (GH rare)

- **Presenting Signs and Symptoms are non-specific**

  Headache, fatigue, anorexia, nausea

  visual changes (uncommon)

- **Diagnostic Evaluation**

  TSH, FT4, 8AM ACTH, cortisol, Cosyntropin stimulation, Glucose, LH, FSH, Testosterone or Estradiol

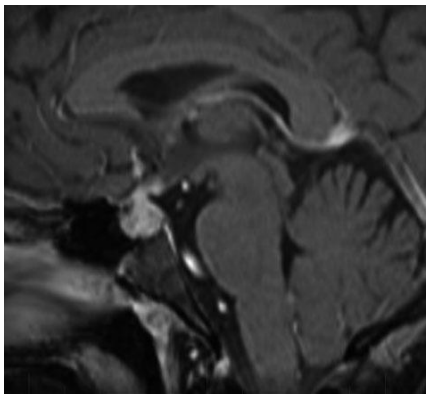
- **Confirmation**
  - **≧1 pituitary deficit (ACTH or TSH) + MRI abnormalities**
  - **≧ 2 pituitary deficit + symptoms (headache or others)**

34

Hypophysitis - MRI

MRI of sella

- **Diffuse pituitary enlargement**
- **Thickening of infundibulum**
- **On post-contrast T1 weighting imaging (T1WI), diffuse homogeneous enhancement of the gland**



35

Consequences

- **Central hypothyroidism >90%**
- **Hypogonadotropic Hypogonadism 83-87%**
- **Central adrenal insufficiency >75%**
- **Panhypopituitarism 50%**

Very rare

36

Consequences

- Central hypothyroidism >90%
- Hypogonadotropic Hypogonadism 83-87%
- Central adrenal insufficiency >75%
- Panhypopituitarism 50%

Anti-PD-L1 Treatment Induced Central Diabetes Insipidus

Chen Zhao, Sri Harsha Tella, Jaydira Del Rivero, Anuhya Kommalapati, Ifechukwude Ebenuwa, James Gulley, Julius Strauss, Isaac Brownell

The Journal of Clinical Endocrinology & Metabolism
Endocrine Society

→ Differentiate from mets

37

Primary Adrenal Insufficiency

CTLA-4 gene located on Ch 2q33

- Graves disease, T1DM, Hashimoto's thyroiditis, Addison's disease

Incidence - Rare

- 43 case out of 5831 pts (0.7%)
- 14 cases >= grade 3 (0.2%)
- 11/262 pts (4.2%) who received combination therapy

Diagnostic Evaluation

- Serum cortisol, ACTH, aldosterone, and renin, (adrenal autoantibodies)

38

Type 1 DM

Incidence
- **13 cases of any grade (0.2%); 12/13 observed in PD-1 inhibitor**
- **6 cases >= grade 3 (0.1%)**
- **Continue ICI after resolving the acute hyperglycemia**

Diagnostic Test
- **GAD Ab, Anti-insulin, anti-islet cell A, Zinc transporter 8, C peptide, insulin**
- **Check use of steroids**

Treatment
- **Based on recognized guidelines**

39

Thyroid Related irAEs

- **Thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroiditis) reported in *6-50*% of patients on ICI**

40

Hypothyroidism

Symptoms can be nonspecific

- **Unexplained fatigue, weight gain, hair loss, cold intolerance, constipation, depression**

Work-up/Labs

- **High TSH, low FT4 (if biochemical hypothyroidism confirmed, obtain TPO as well)**

41

Hyperthyroidism

May be secondary to thyroiditis or from Graves Disease

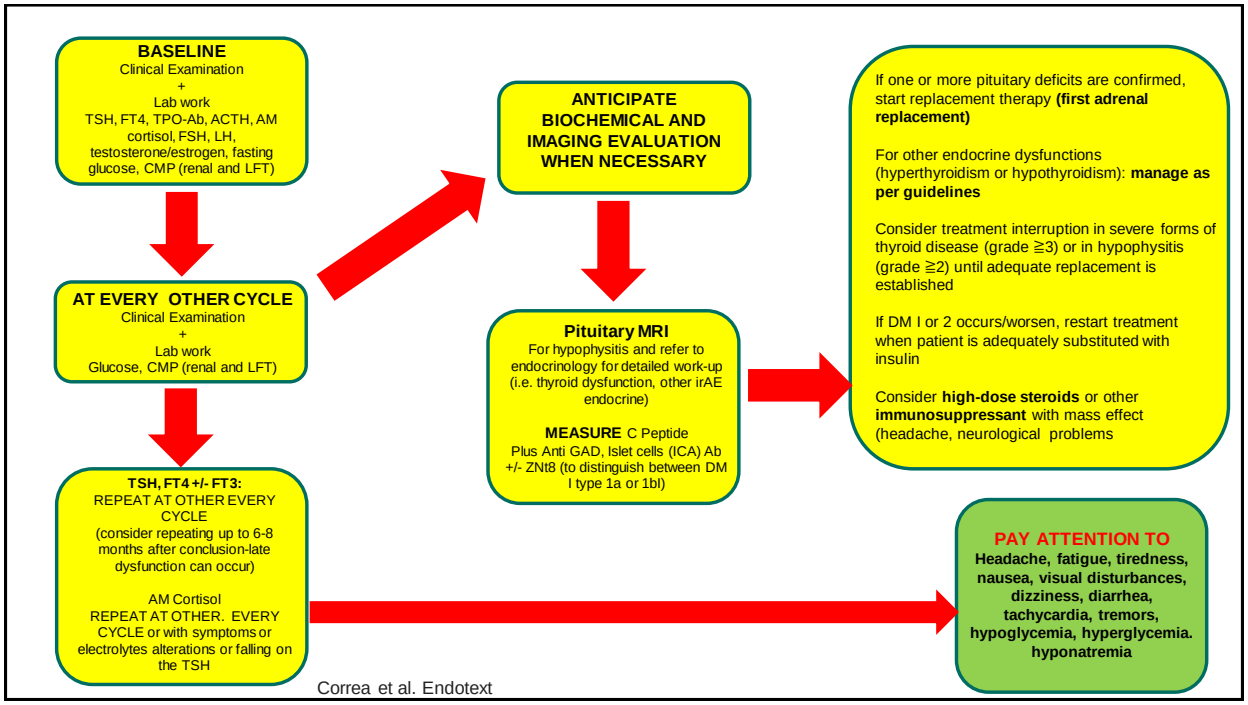
Thyroiditis

- **Most frequent cause of thyrotoxicosis in ICI therapy**
- **Seen more commonly with anti PD1/PDL1 drugs**

Graves' Disease

- **Very rare**
- **Occurs more with CTLA-4 drugs**

42



Correa et al. Endotext

43

Principles of Management of Endocrinopathies

- Patient education on potential irAE
- Establish physician network
- Short-term adverse events from GC use
- Long-term GC use adverse events

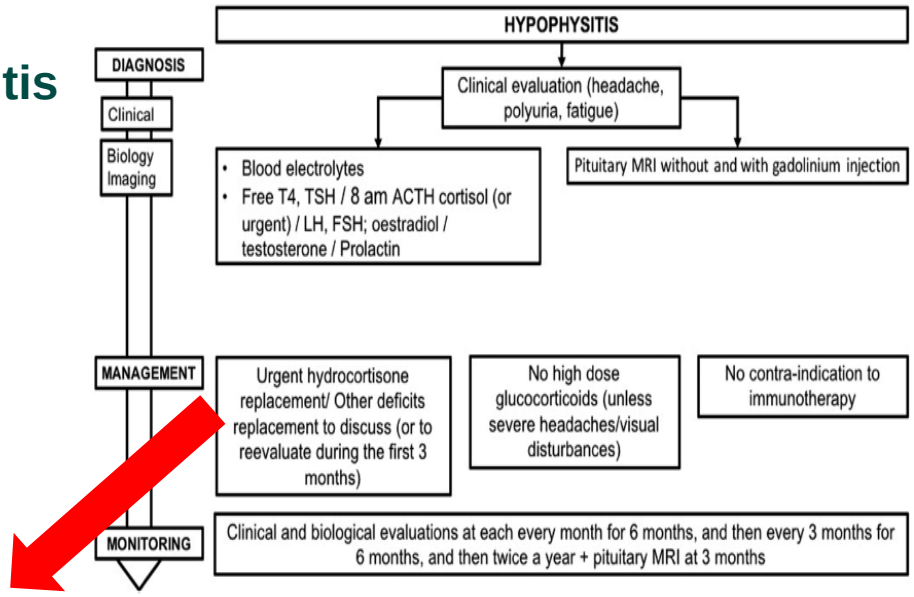
44

General Treatment Guideline for Low Grade irAE

Grade	Corticosteroid Use	Notes
1	• Corticosteroids not usually indicated	• Continue Immunotherapy
2	• If indicated, oral prednisone 0.5-1mg/kg/day or IV methylprednisolone 0.5-1mg/kg/day • If no improvement in 2-3 days, increase to 2mg/kg/day • Once improved, start 4-6 week steroid taper	• Hold immunotherapy during corticosteroid use • Restart immunotherapy once resolved <= Grade 1 and off CS • Start PPI for GI PPX
3	• Start prednisone 1-2mg/kg/day or methylpred • If no improvement in 2-3 days, alternate/add'l immunosuppressant • Supportive Tx	• Hold immunotherapy; if no improvement in 4-6 weeks, discontinue immunotherapy • Consider IV CS • Start PPI for GI PPX • Add PCP ppx if more than 3 weeks of immunosuppression expected (>30mg pred/day)
4	• Start prednisone 1-2mg/kg/day or methylpred • If no improvement in 2-3 days, alternate/add'l immunosuppressant (e.g. infliximab) • Supportive Tx	• Discontinue immunotherapy • Continue IV CS • Start PPI for GI PPX • Add PCP ppx if more than 3 weeks of immunosuppression expected (>30mg pred/day)

45

Hypophysitis



If central AI

- **Start HC 10-12mg/m^2**

46

Hypophysitis

- If central hypothyroidism
  - Start LT4 1.2mcg/kg
  - Repeat TFT 6 wks after then periodically to assess recovery
- If central hypogonadism
  - Repeat levels in 2-3 months and consider testosterone in men or HRT in women
  - If GH deficiency: NO REPLACEMENT

Puzanov et al. Journal for ImmunoTherapy of Cancer (2017) 5:95

47

Hypophysitis

For severe or life-threatening symptoms (adrenal crisis, severe headache, visual field deficiency)

- Hospitalize
- High dose GC (prednisone 1-2mg/kg/day or equivalent methylprednisolone) followed by taper over 1 month
- Use of immunosuppressant like infliximab, mycophenalate, etc, if necessary (low evidence)
- If central hypothyroidism, replace LT4 after GC treatment initiation

Puzanov et al. Journal for ImmunoTherapy of Cancer (2017) 5:95
Ruggieri et al. Journal of Endocrinological Investigation (2019) 42:745–756

48

Primary Adrenal Insufficiency

Acute Clinical Suspicion

- **Diagnostic tests**
- **Do not delay treatment with stress dose GC**
- **R/O Infection**

Chronic Symptoms

- **Diagnostic tests**
- **Treat with physiologic dose hydrocortisone and fludrocortisone**

49

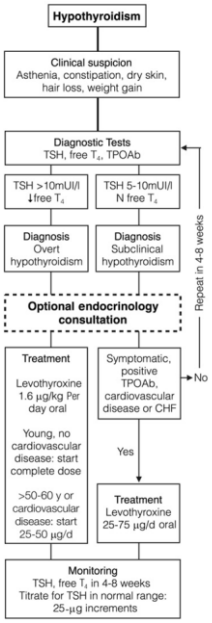
Hypothyroidism

Treatment

- **Overt hypothyroidism: treat with levothyroxine dose (1.2 µg/kg per day)**
- **Subclinical hypothyroidism: treatment is usually not necessary unless the patient becomes symptomatic, anti-TPO Abs are positive, or the patient has a history of cardiovascular disease or heart failure.**
  - **In this setting, lower doses of levothyroxine are needed to achieve normal TSH**

Monitoring

- **TSH monitoring recommended 4–8 weeks after starting or titrating treatment until normal range is reached**

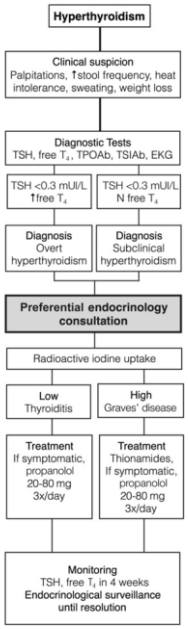


50

Hyperthyroidism

Thyroiditis

- **Conservative management is usually sufficient**
- **Non-selective beta blockers as needed for symptomatic patients during hyperthyroid phase**
- **Self limited process, can lead to permanent hypothyroidism 1-2 months after thyrotoxic phase**
- **Concurrent adrenal insufficiency should be excluded with a cortisol level in patients beginning thyroid hormone replacement therapy when hypothyroid (to evaluate for hypophysitis)**



51

Take Home Points ICI

- **Recognize endocrine immune related adverse events in patients on ICI therapy**
- **An awareness of the symptoms and management of immune-related endocrine events may aid in the safe and appropriate use of immune checkpoint inhibitors**
- **Management includes close patient monitoring, appropriate laboratory testing for endocrine function, replacement of hormones**
- **Stopping ICI therapy is usually not recommended except in cases of life-threatening endocrine toxicity which are unsuitable for efficient treatment**
- **Even in cases of life-threatening endocrine toxicity, discontinuation of therapy and reintroduction after recovery should be discussed**

52

Case 2

62-year-old man is being seen in the ED. **His history is notable for a widely metastatic melanoma; he recently completed his third cycle of chemotherapy with nivolumab combined with ipilimumab.**

Over the past week, he has grown increasingly fatigued, with additional complaints of nausea, myalgias, and a mild headache (3/10 in intensity).

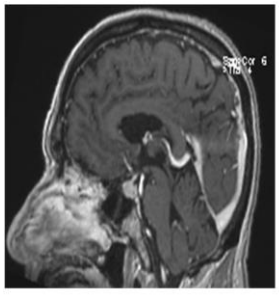
The patient's medical history is otherwise notable for type 2 diabetes and hypertension. His current medications include insulin glargine 50 units every night at bedtime, metformin 1,000 mg twice a day, and lisinopril 40 mg. **His fasting blood glucose concentration has been 70 to 80 mg/dL over the past week**; these values are much lower than normal for him.

On examination, his BMI 28 kg/m^2, BP 128/76 mmHg, and HR is 80 beats/min. The patient appears tired. Extraocular movements are intact, pupils are equally reactive, and visual fields are full to confrontation. The patient overall appears euvolemic.

The only notable examination finding is a healed incision on the back where his initial melanoma was removed.

53

Laboratory Test	Patient Result	Normal Value
Sodium	**132 mEq/L (132 mmol/L)**	135-145 mEq/L (135-145 n
Creatinine	0.8 mg/dL (70.7 µmol/L)	0.8-1.2 mg/dL (0.8-1.2 µmo
Glucose	160 mg/dL (8.9 mmol/L)	70-140 mg/dL (70-140 mg/
Hemoglobin A1c	8.0%	4%-5.6%
Adrenocorticotropic hormone	**6 pg/mL (1.3 pmol/L)**	7-63 pg/mL (1.5-14 pmol/L)
Cortisol at 10:30 AM	**1.1 µg/dL (30.3 nmol/L)**	7-25 µg/dL (193-690 nmol/L
Thyroid-stimulating hormone	1.0 mIU/L	0.5-4.5 mIU/L
Free thyroxine	**0.3 ng/dL (3.8 pmol/L)**	0.75-1.5 ng/dL
Urine osmolality	400 mOsm/kg	150-1150 mOsm/kg



54

Which of the Following Is the Most Appropriate Next Step in Management?

A. Discontinuation of nivolumab/Ipilimumab chemotherapy
B. Stress dose of hydrocortisone with subsequent initiation of levothyroxine
C. Physiological dose of hydrocortisone with subsequent initiation of levothyroxine
D. Transsphenoidal biopsy of the pituitary for diagnostic purposes

Rationale

ICI hypophysitis is an increasingly common phenomenon in patients treated with newer chemotherapeutic agents that target CTLA4 or PD-1/PDL-1. Combination therapy (eg, CTLA-4 inhibitor + PD-1 inhibitor) seems to confer the highest risk, with meta-analyses suggesting an incidence rate of 6.4%.

Hyponatremia is a common finding, presumably related to SAI deficiency and/or secondary hypothyroidism. MRI typically demonstrates a moderately enlarged and enhancing pituitary gland (normal in 30%)

Management of ICI hypophysitis involves supportive care and appropriate hormonal replacement.

Patients with hemodynamic instability from adrenal crisis, or with very severe mass effect symptoms (eg, incapacitating headache, optic chiasm compression), can be treated with high-dose glucocorticoids.

Limited data to date do not show improvement in clinical outcomes for high-dose glucocorticoid treatment compared with normal physiologic dosing of glucocorticoids

Which Statement Is Correct About ICI-induced Dysthyroidism?

A. Most common presentation is hyperthyroidism to Graves disease.
B. TPO and Thyroglobulin antibodies are not elevated.
C. Patients who develop grade 2 IrAE should have the ICI treatment suspended and be started on high dose glucocorticoid.
D. Most patients with initial thyrotoxicosis will later develop hypothyroidism.

Which Statement Is Correct?

A. Hypophysitis is more common with anti. PDL-1 agents.
B. Diabetes mellitus has not been reported with anti-PD-1 agents.
C. Patients who develop grade-2 irAE should have their ICI held and be started on high dose glucocorticoids.
D. Patients who develop irAE are best managed through close communication with the patient and oncologist.

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