Emerging Endocrinopathies Induced by Immune Checkpoint Inhibitors

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Objectives

- Raise awareness of endocrine immune-related adverse events (irAEs) resulting from immune checkpoint inhibitors (ICPi) that are used to treat different cancers

- Recognize the clinical presentation and natural course of the most common endocrine irAEs: hypophysitis and thyroiditis

- Discuss appropriate management strategies for hypophysitis and thyroiditis cases

Disclosures

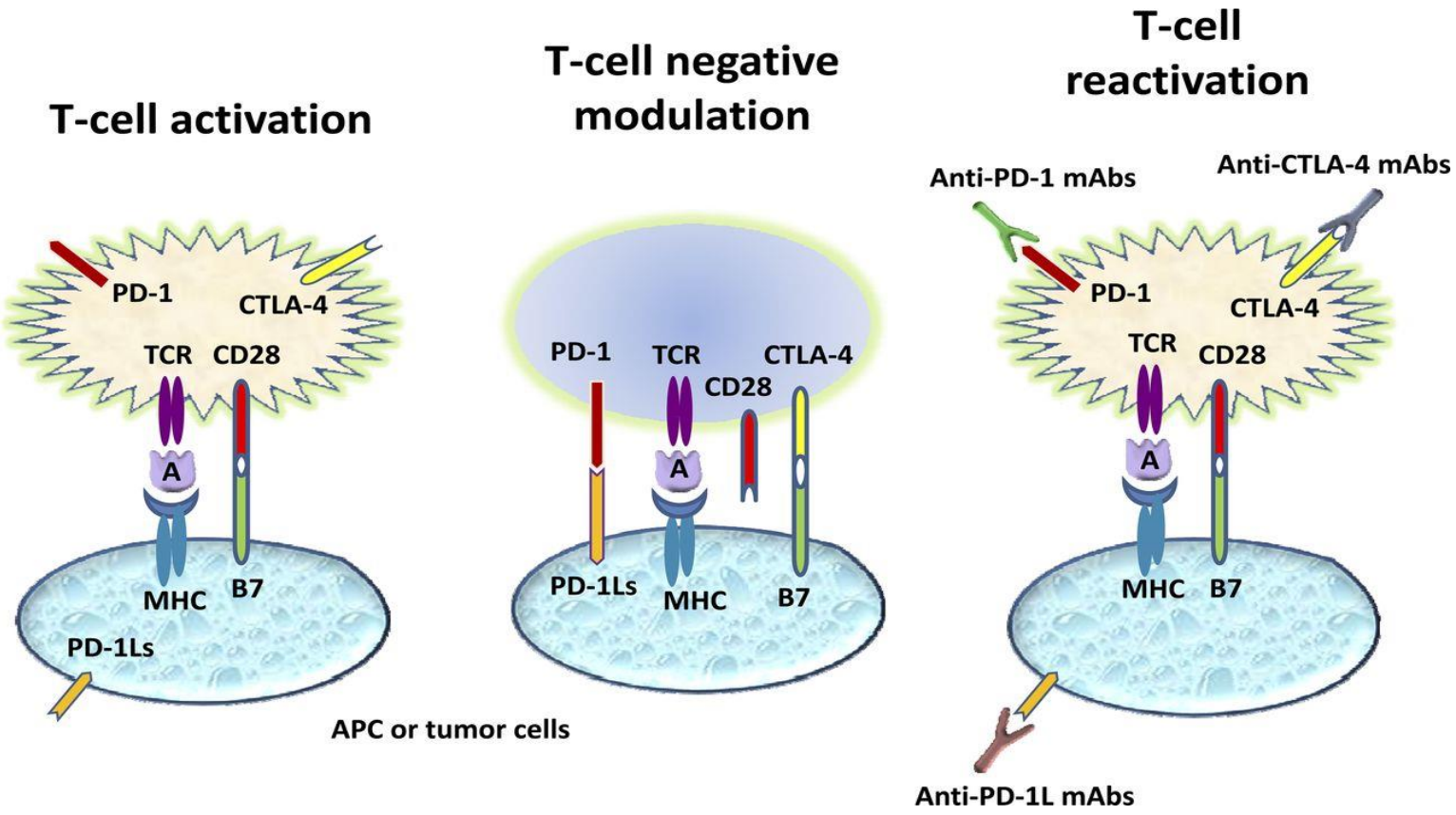
- None

Introduction

- Immune checkpoints are small molecules on the cell surface of T- lymphocytes
- Immune checkpoints play critical roles in maintaining immune homeostasis and self-tolerance and modulating the duration and amplitude of physiological immune responses
- In recent years, progress has been made in cancer immunotherapy by developing immune checkpoint inhibitors that act by restoring the ability of the immune system to detect and destroy cancer cells
- Immune checkpoint inhibitors have shown remarkable benefit in the treatment of full range of cancer types
- Immune checkpoint inhibitors are anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody and anti-programmed cell death-1 (PD-1) antibodies and anti-programmed cell death-1 ligand (PD-L1) antibodies

Endocrine Reviews, Volume 40, Issue 1, February 2019, pages 17-65

Mechanism of Action of Immune Checkpoint Inhibitors



The Journal of Clinical Endocrinology & Metabolism, Volume 98, Issue 4, 1 April 2013, Pages 1361–1375

Immune Checkpoint Inhibitors Approved by FDA

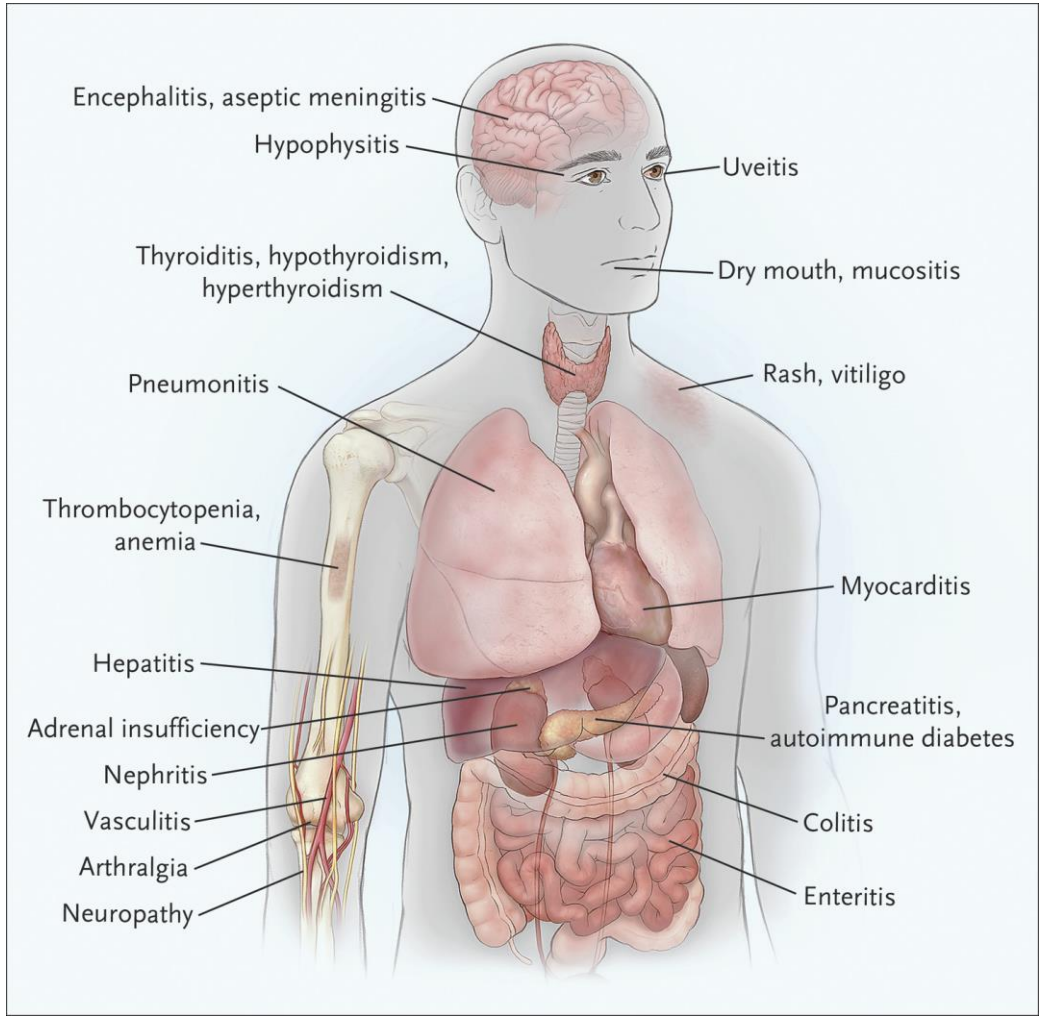
Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non-small cell lung cancer, renal cell carcinoma, hepatocellular carcinoma…
Pembrolizumab	PD-1	Melanoma, non-small cell lung cancer, classic Hodgkin's lymphoma…
Atezolizumab	PD- L1	Non-small cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	urothelial carcinoma

MA Postow et al. N Engl J Med 2018;378:158-168

Immune-Related Adverse Events (irAEs)

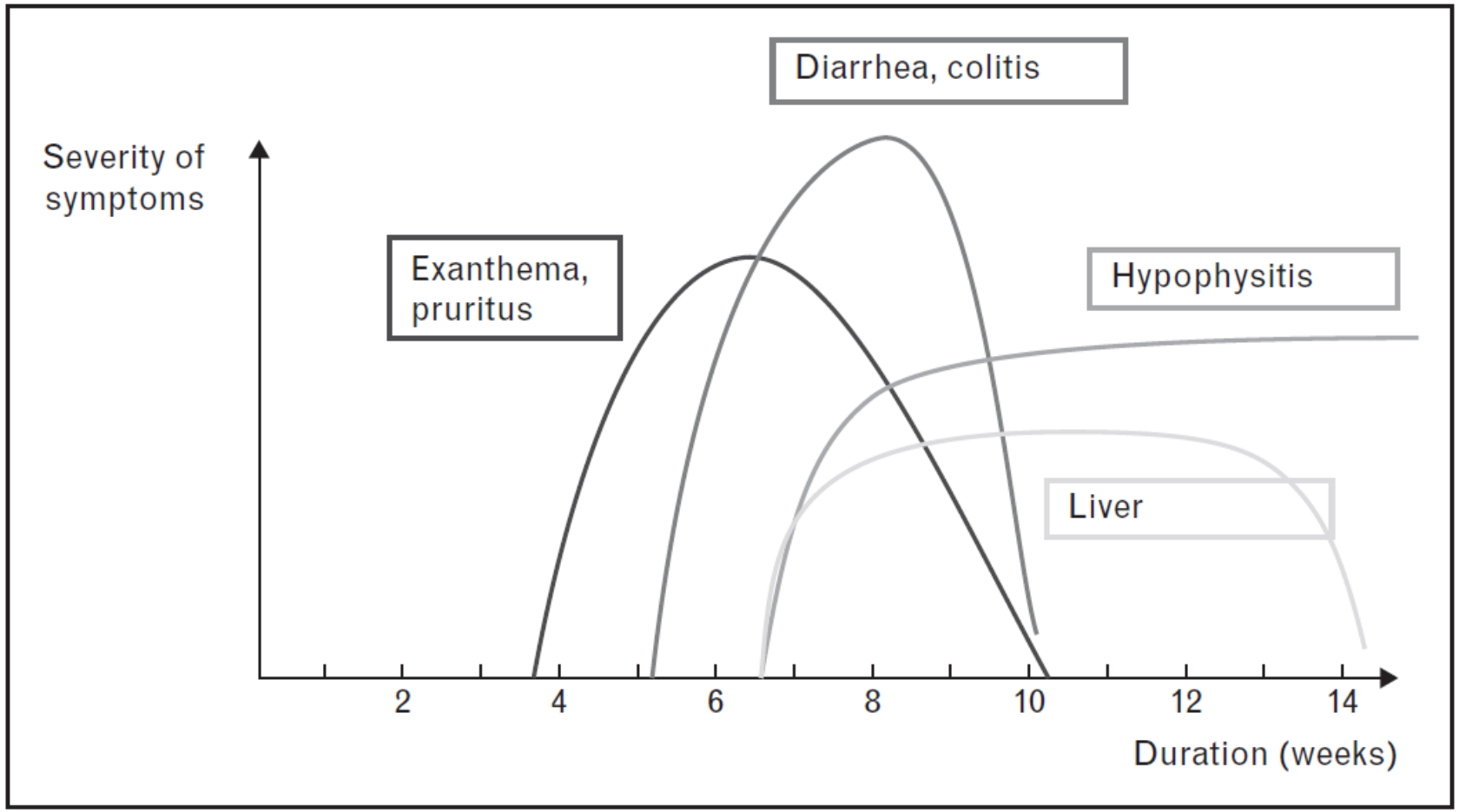
- The limitations of using immune checkpoint inhibitors include the development of a unique set of inflammatory side effects
- These side effects referred to as irAEs
- The precise pathophysiology underlying irAEs is unknown however autoimmunity is the suggested mechanism sustaining these toxicities
- It can result in inflammation of any organ

Organs Affected by Immune Checkpoint Inhibitors



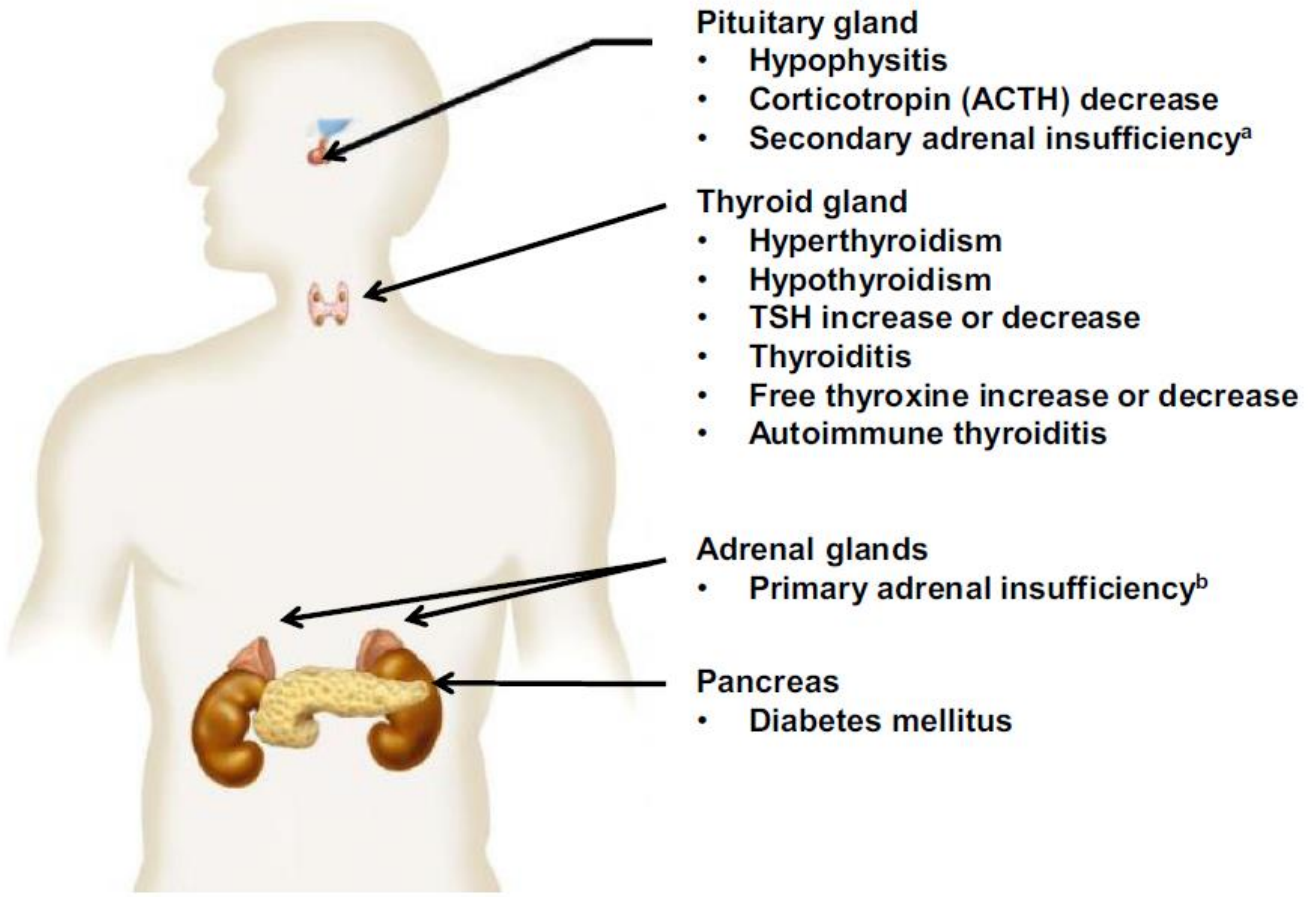
MA Postow et al. N Engl J Med 2018;378:158-168

Time Course of irAEs During Therapy with Cytotoxic T-lymphocyte Antigen-4 Antibody



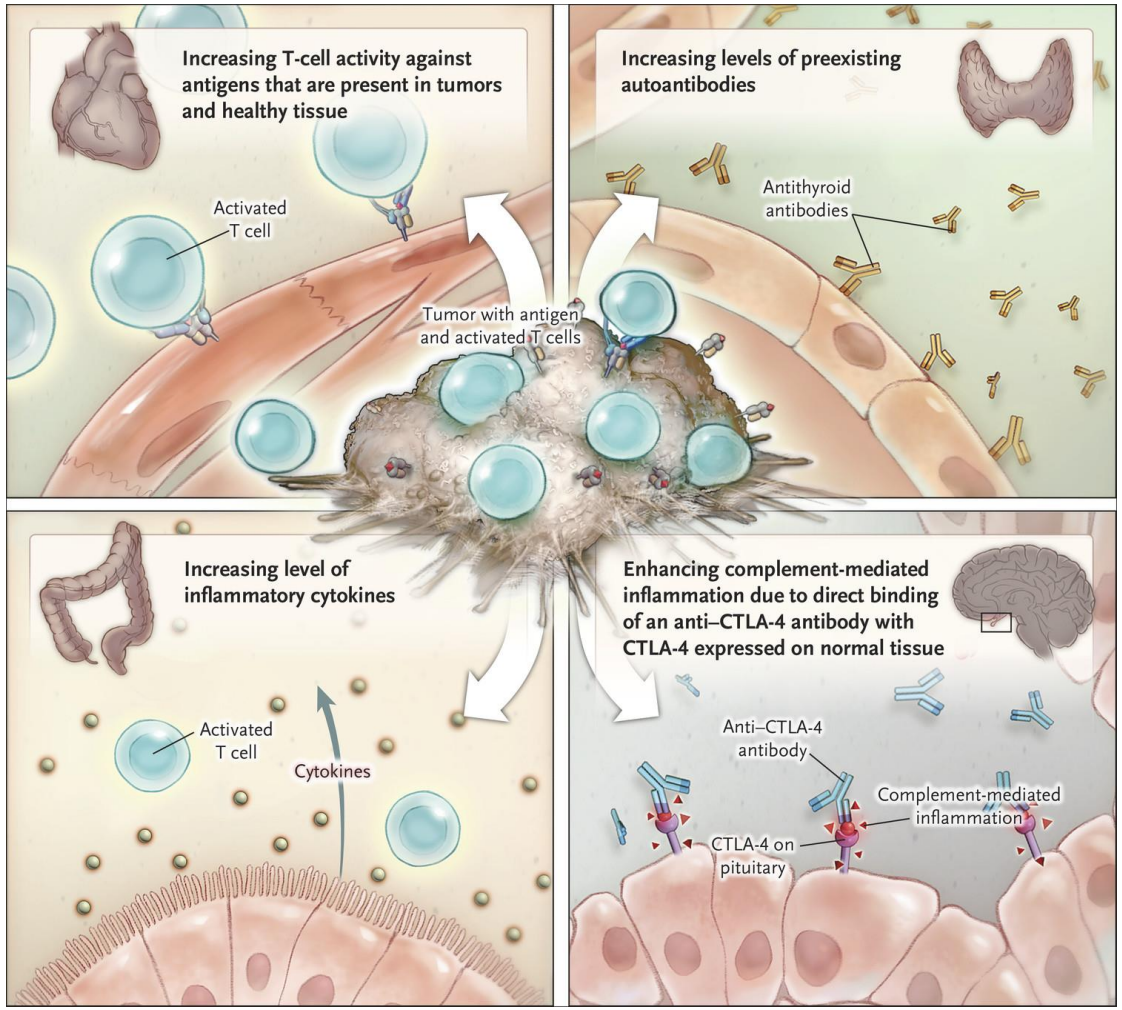
Curr Opin Endocrinol Diabetes Obes 2012, 19:314–321

Major Endocrine Events Associated with Immune Checkpoint Inhibitors



M.Sznol et al./Cancer treatment reviews 58 (2017) 70-76

Possible Mechanisms Underlying irAEs



MA Postow et al. N Engl J Med 2018;378:158-168

Key Points for Endocrine irAEs

- Typically have a delayed onset and prolonged duration
- The pituitary, thyroid, and adrenal glands are the endocrine organs that are typically affected by immune checkpoint inhibitors
- Some may be life-threatening if not recognized early
- Endocrinopathies are not resolved and the function of the gland is often permanently damaged however could be treated with hormone replacement
- Effective management depends on early recognition and prompt intervention
- Oncologists, endocrinologists, emergency medicine physicians, and primary care physicians should be vigilant for these irAEs and coordination of care is very important

Common Terminology Criteria for Adverse Events Grading Criteria

Endocrine disorders	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypophysitis	Asymptomatic or mild symptoms, intervention not indicated	Moderate, Minimal, local or noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences, urgent intervention indicated	Death
Hyperthyroidism Hypothyroidism Thyroiditis	Asymptomatic, clinical or diagnostic observations only	Moderate intervention indicated	Severe symptoms, limiting self-care, hospitalization indicated	Life-threatening consequences, urgent intervention indicated	Death

United States National Cancer Institute, Common Terminology Criteria for Adverse Events, 2017

Case Presentation 1

- A 55-year-old female patient with history of metastatic melanoma presented with severe headache, change in mental status per daughter, weakness, and fatigue
- This presentation was one week after receiving the third cycle of ipilimumab therapy
- Patient reported nausea and feeling very tired
- She was diagnosed with invasive rectal melanoma 1 year before presentation
- She underwent tumor resection, she was found to have 3.5 cm ulcerating mass adherent to the vaginal wall
- Further diagnostic workup revealed metastasis to the lung and left inguinal lymph node
- Brain magnetic resonance imaging 3 months before presentation revealed no evidence of brain metastasis

Case Presentation 1

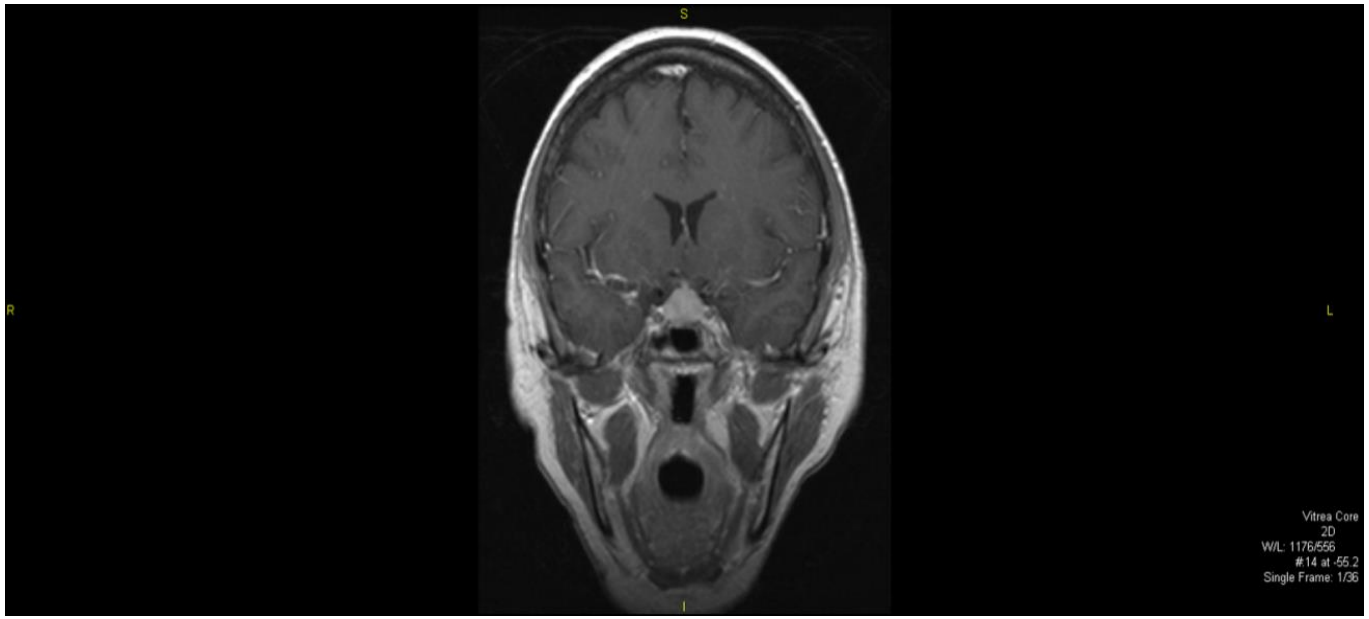
- She received 3 cycles of ipilimumab 3 mg/kg IV, which is given every 3 weeks, last cycle was one week before presentation

- Physical exam was remarkable for hypotension and tachycardia. She was alert and oriented to place and person only

Summary of Labs

	ACTH (6-58)	**Cortisol**	**TSH (4-4.5)**	**FT4 (0.8-1.8)**
Before Therapy	9	25	2	1.3
After 3 cycles	**<2 ↓**	**0.8 ↓**	**0.1 ↓**	**0.7 ↓**

MRI Findings



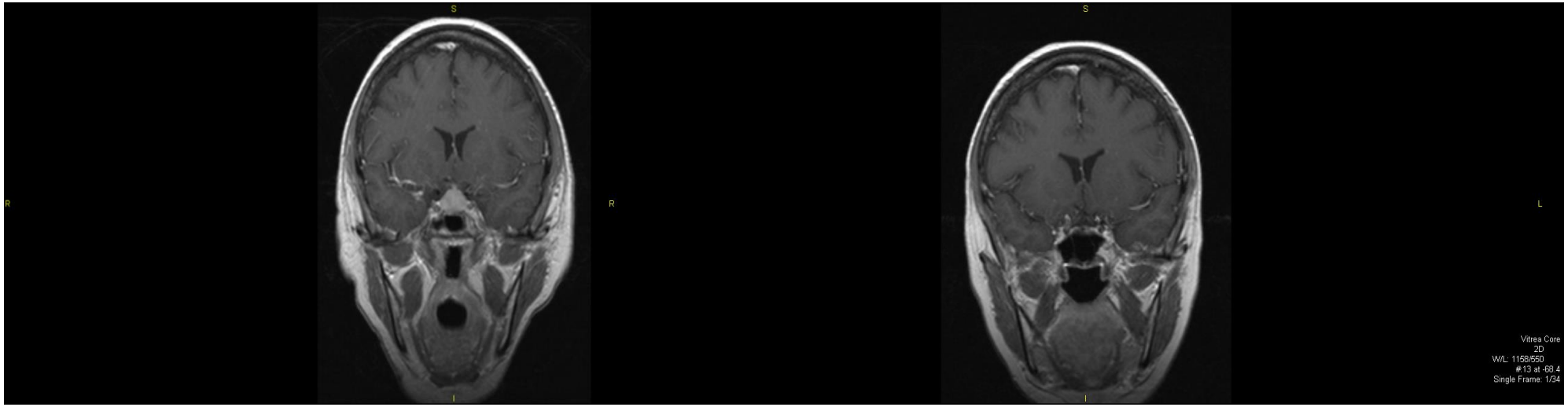
Case Presentation 1

- Ipilimumab induced autoimmune hypophysitis was suspected causing secondary adrenal insufficiency and central hypothyroidism
- Patient was started on prednisone 60 mg daily tapered to 20 mg daily over few days and then she was started on physiological doses of hydrocortisone
- Levothyroxine 88 µg daily was started
- Ipilimumab was discontinued. Patient received Wnt Inhibitor therapy for melanoma

Follow up MRI

After 3 cycles of treatment

3 months later



Case Presentation 1

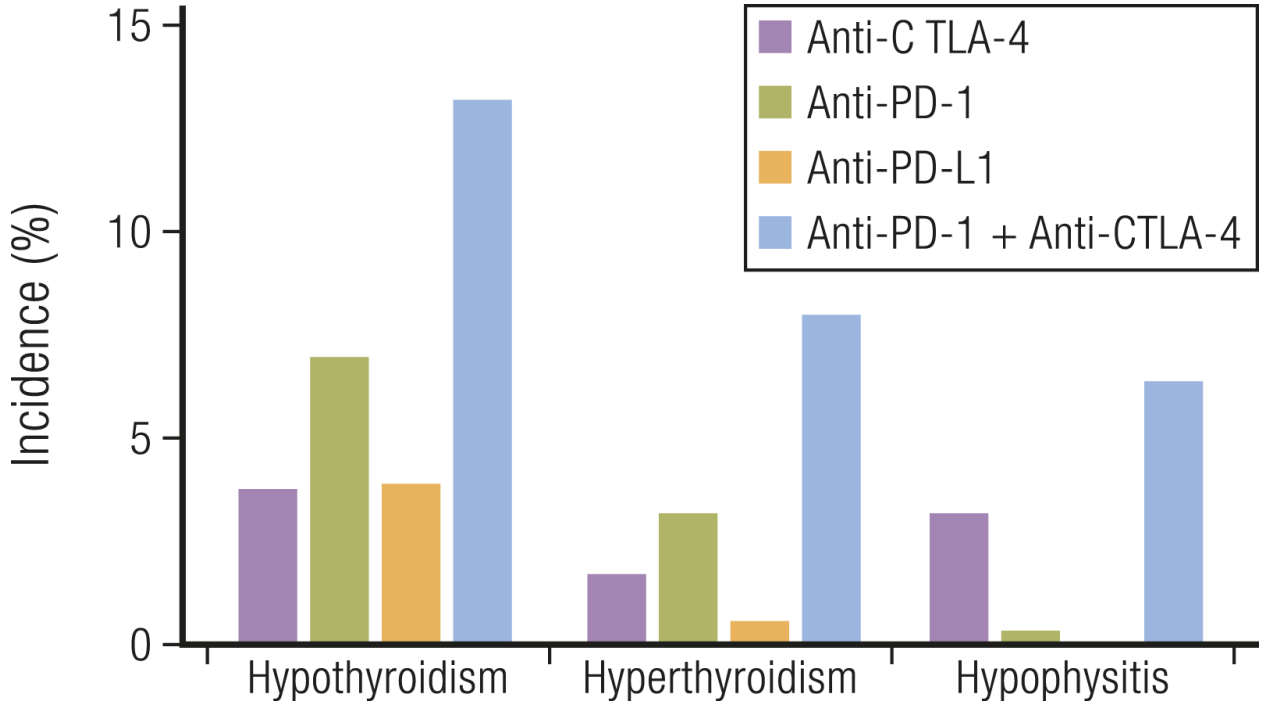
- Cosyntropin stimulation test was done every 6 months for 2 years
- Patient continued to have low cortisol levels requiring physiological replacement of hydrocortisone
- Multiple attempts has been made to lower levothyroxine however she continued to have low free T4

Immune-Related Hypophysitis (IH)

- Hypophysitis is inflammation of the pituitary gland
- It is rare condition in the general population
- It is one of the most common endocrine irAEs associated with immune checkpoint inhibitors
- Prevalence varies from 1% to 17%
- Occurs mainly in patients treated with ipilimumab alone or with combination ipilimumab-nivolumab therapy
- It has been reported at higher rates among men and older age

Endocrine Reviews, Feb 2019, 40(1):17-65
JCEM, Nov 2014, 99(11):4078-4085
Clinical Endocrinology (2016) 85, 331-339

Incidence of thyroid dysfunction and hypophysitis induced by different ICPi



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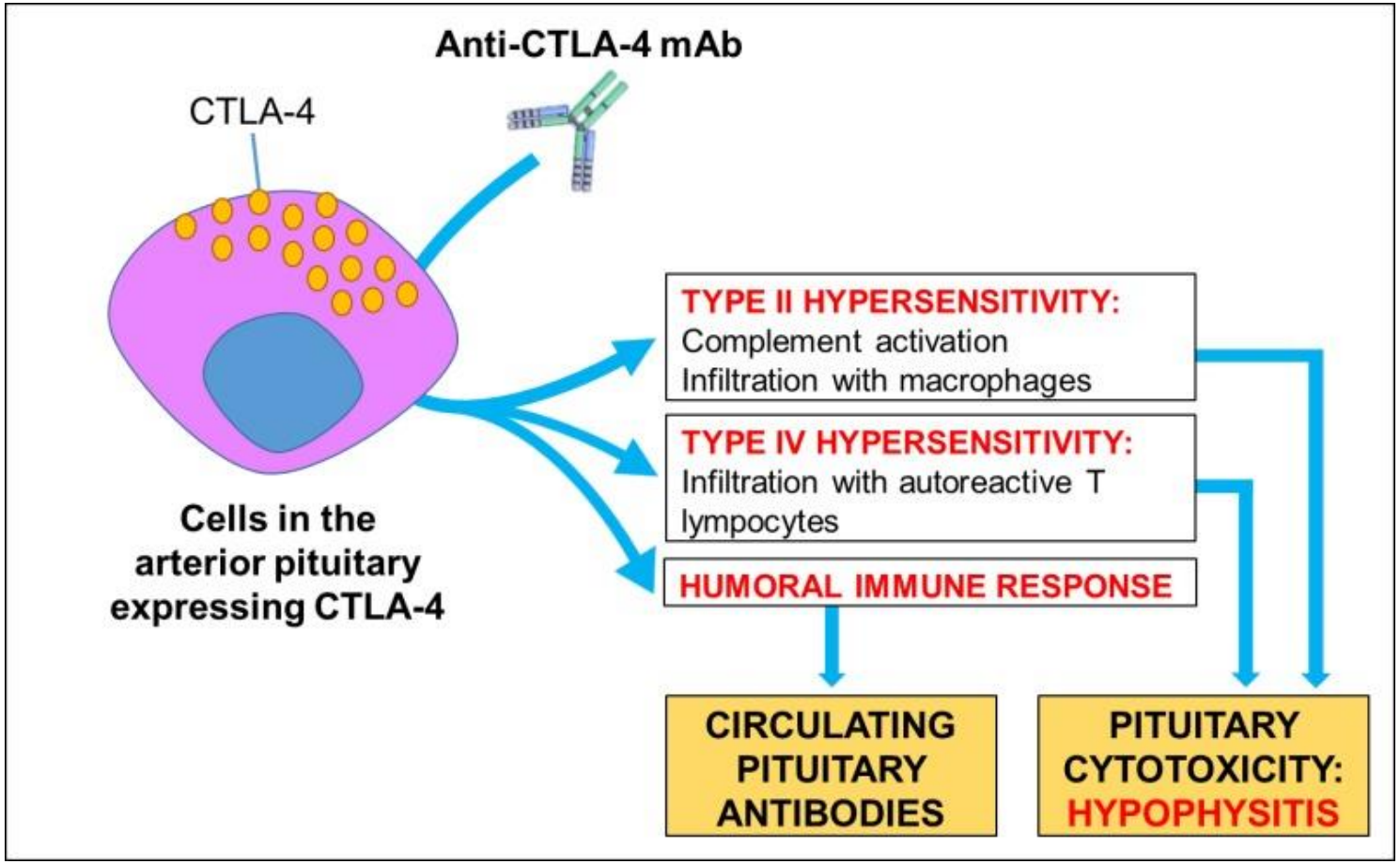
Pathophysiology of ICPi-related Hypophysitis



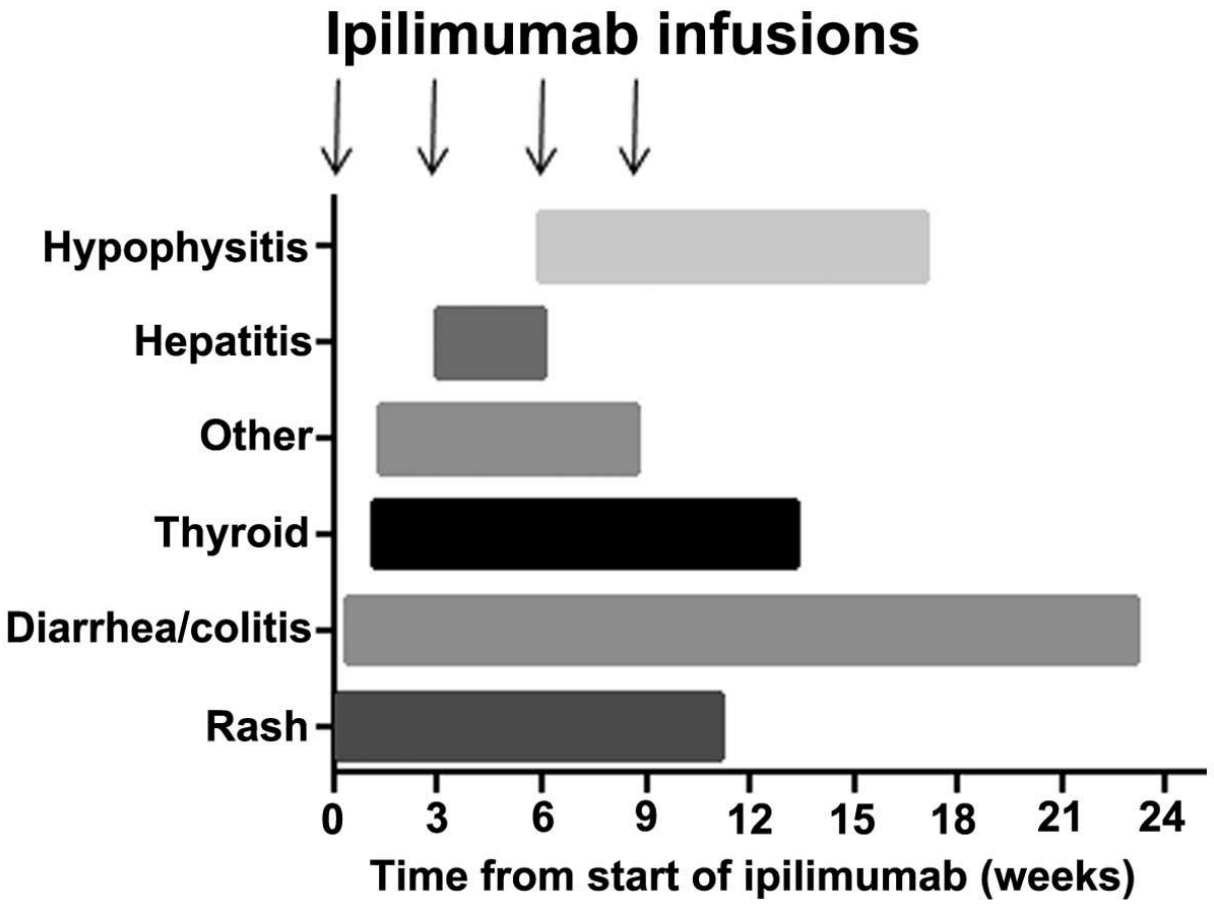
Endotext August 2018

Clinical Manifestations of IH

- Headache and fatigue are the most common presenting symptoms
- Other symptoms include nausea, anorexia, dizziness, unintentional weight loss, and cold intolerance
- In contrast to other forms of pituitary lesions or masses, symptoms due to mass effect such as visual deficits are rare in IH
- Ipilimumab-induced hypophysitis presents typically 2-3 months after starting treatment or after the third cycle of starting ipilimumab

Endocrine-Related Cancer, 21, 371-381

Average Time to Develop irAEs for Patients Treated with Ipilimumab



Oncology Letters 11: 1581-1585, 2016

Biochemical Findings in Patients with IH

- Central hypothyroidism is one of the most common anterior pituitary hormone deficiency

Usually there is progressive decline in thyroid-stimulating hormone

Patients usually have low free T4 in the setting of inappropriately low or normal thyroid-stimulating hormone

Should be differentiated from non-thyroidal illness or euthyroid sick syndrome

- Central adrenal insufficiency is also common: low cortisol level in the setting of inappropriately low or normal ACTH

- Hypogonadism
- Hyponatremia
- hypoprolactinemia
- Diabetes insipidus is not common

Radiologic Findings of IH

- Pituitary enlargement on magnetic resonance imaging
- Thickening of the pituitary stalk
- Impingement on the optic chiasm is rare
- Contrast enhancement may be homogeneous or heterogeneous
- Interesting enough, pituitary enlargement may precede the clinical diagnosis of hypophysitis by several weeks

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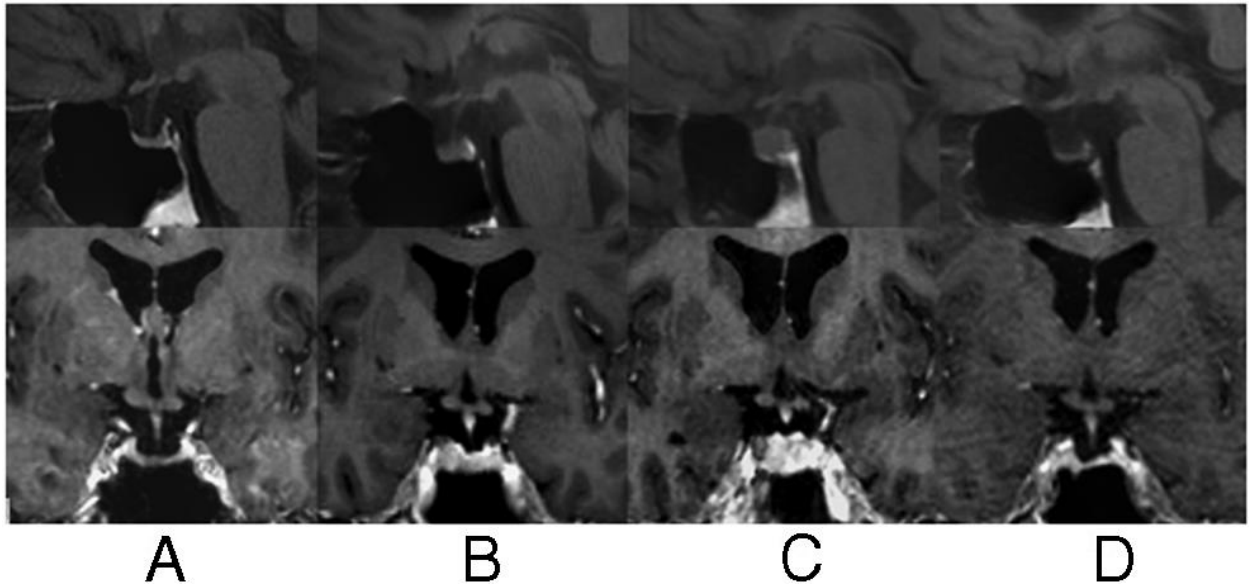
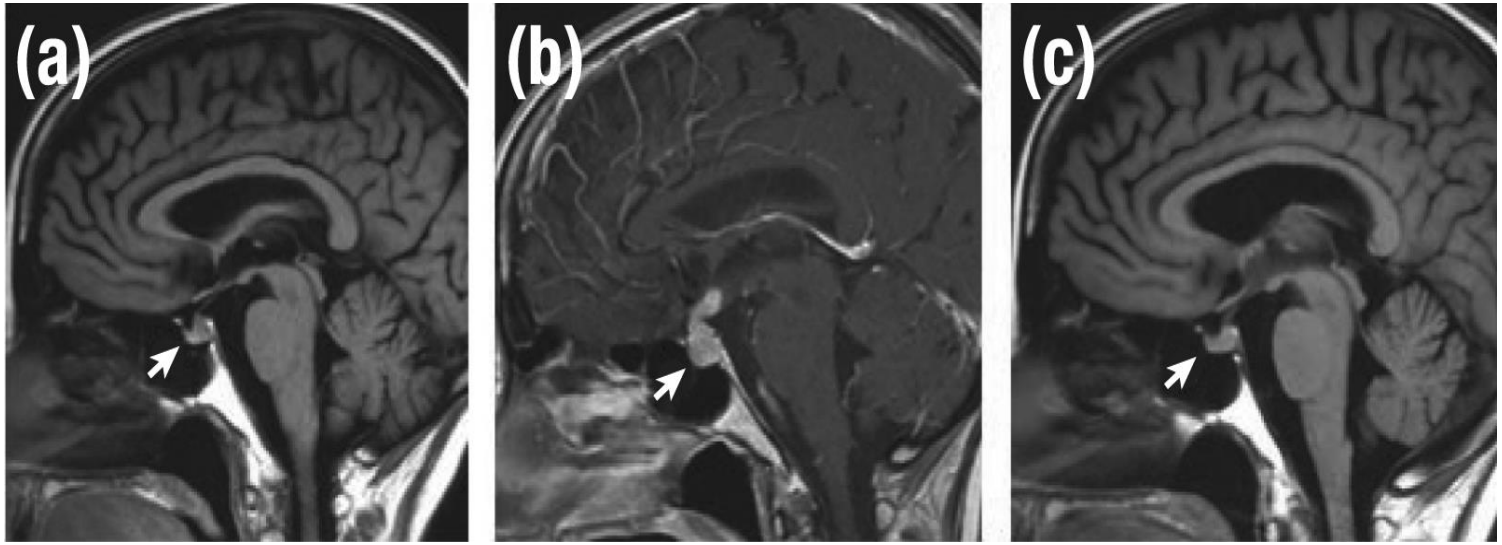
Pituitary enlargement and resolution in a 59-year-old male with IH.



The Journal of Clinical Endocrinology & Metabolism, Volume 99, Issue 11, 1 November 2014, Pages 4078–4085,

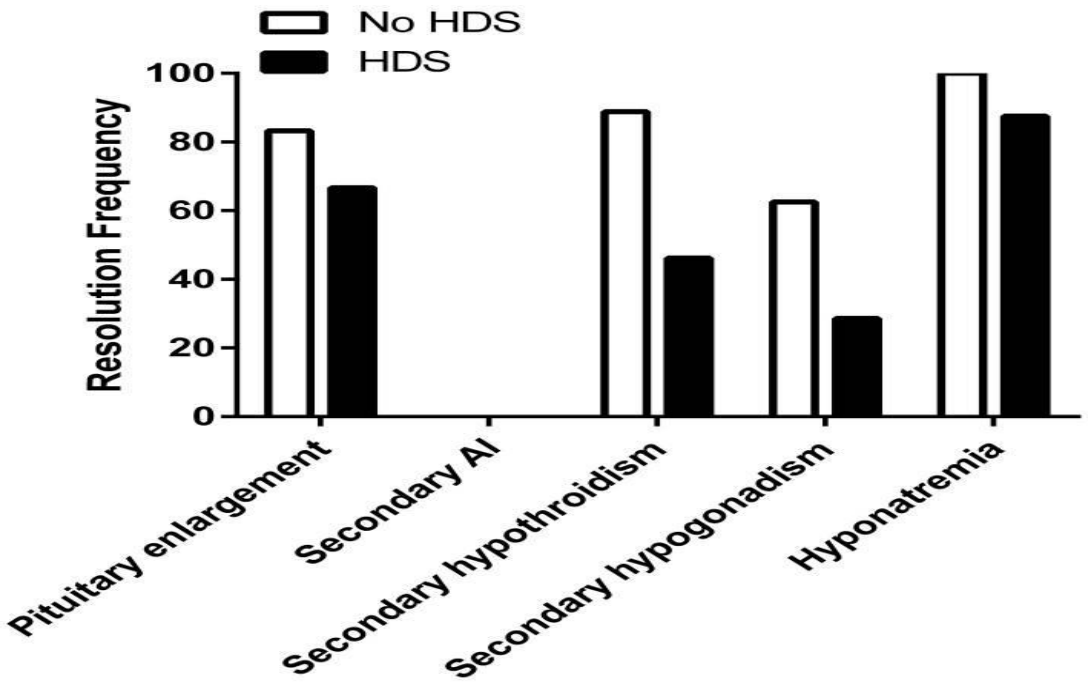
ICPi-related hypophysitis. Brain MRI showing development and resolution of ICPi-related hypophysitis



Endocrine Reviews, Volume 40, Issue 1, February 2019, Pages 17–65,

Management of IH

- Management basically includes replacement of deficient hormones(physiological doses of steroids and thyroid hormone)
- High doses of steroids may be necessary in the setting of severe headaches, vision changes, and or adrenal crisis
- In some studies, treatment with higher doses of steroids did not seem to improve pituitary function recovery compared with physiological doses of steroids Clin Cancer Res. 2015 Feb 15; 21(4): 749-755



Prognosis for Pituitary Recovery

- Both adrenal insufficiency and hypothyroidism seem to represent long-term sequelae of hypophysitis
- Lifelong hormonal replacement is needed in most cases
- Recovery of thyroid hormone was noted in small percentage of patients

The Journal of Clinical Endocrinology & Metabolism, Volume 99, Issue 11, 1 November 2014, Pages 4078–4085

SAT-616

One Year Follow-up of A Patient With Ipilimumab-induced Hypophysitis

- Leah Giaccotto DO, Tyler Moore, MD, Omar Zmeili, MD
- Summa Health System – Akron, OH

Introduction

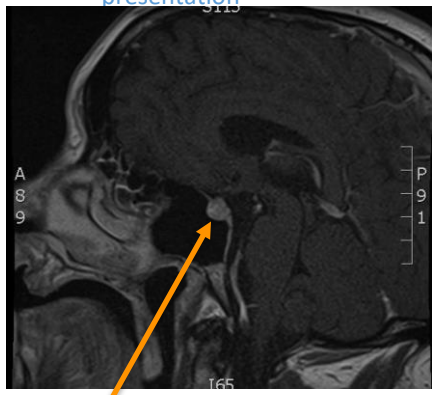
- Ipilimumab, a monoclonal antibody to cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), is a novel therapeutic advance in the treatment of certain cancers including metastatic melanoma.
- Autoimmune hypophysitis secondary to ipilimumab has been reported as the most common endocrinopathy which is increasing in frequency.

Clinical Case

- A 45-year -old male presented to an outpatient endocrinology office with new onset fatigue and headaches after being treated with Ipilimumab for metastatic melanoma.
- Patient had started chemotherapy treatment with Ipilimumab about two months prior. Thyroid studies as well as cortisol and ACTH levels were monitored regularly during his treatment.
- Originally, his TSH and Free T4 levels were within the normal ranges. After our patient's third dose of Ipilimumab, he started to complain of headache and fatigue.
- Laboratory evaluation showed a low TSH level of 0.153 mIU/mL (normal range, 0.358-3.740), low Free T4 level of 0.52 ng/dL (normal range, 0.76-1.46), low ACTH level of 3 pg/dL (normal range, 7-69) and low cortisol level 1.0 mcg/dL (normal range, 2.9-17.3).
- At this point, the patient was referred to our office for concern for hypophysitis.
- At our office, repeat thyroid studies were obtained, which again indicated central hypothyroidism with TSH of 0.342 and Free T4 of 0.60.
- Pituitary magnetic resonance imaging (MRI) demonstrated diffuse homogenous enlargement of the pituitary gland.
- Autoimmune hypophysitis secondary to anti-CTLA-4 monoclonal antibody was diagnosed.
- Ipilimumab was discontinued, and he was started on tapering doses of prednisone starting at 100 mg daily as well as levothyroxine 75 mcg daily.
- Patient's symptoms began to improve with steroid treatment. Prednisone dose eventually tapered down and changed to hydrocortisone 10 mg twice daily.

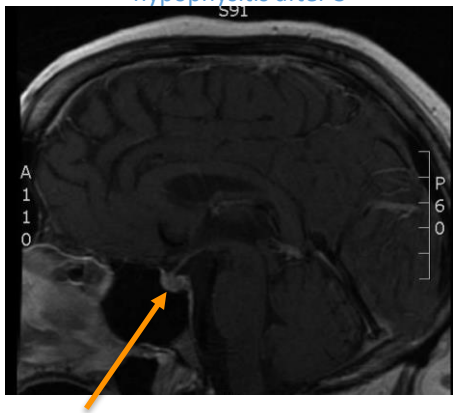
Results

Figure 1 – MRI brain showing hypophysitis at time of presentation



Enlarged pituitary gland with heterogenous internal texture and indistinctness of the anterior portion of the stalk. Anterior displacement of infundibulum

Figure 2 – MRI brain showing resolving hypophysitis after 3



Post contrast enhancement is more homogenous. Infundibulum no longer displaced anteriorly.

Table 1 – Cosyntropin Stimulation Test

	First Test At Presentation	Second Test After 6 months	Third Test After 1 year	Normal Range
ACTH	<5	<5	7	7 - 69
Cortisol Before Cosyntropin	<1	<1	<1	AM: 2.9 – 17.3 PM: 3.7 – 19.4
60 min Cortisol After Cosyntropin	<1	<1	<1	

Clinical Case Continued

- Three months later, repeated pituitary MRI revealed resolution of the pituitary gland abnormality.
- Patient was weaned off levothyroxine after 3 months and thyroid function tests continue to be normal without thyroid hormone replacement.
- Hydrocortisone was decreased to 10 mg every morning and 5 mg every afternoon.
- Cosyntropin stimulation tests obtained 6 months and one year after diagnosis were consistent with chronic secondary adrenal insufficiency.
- Patient is maintained on physiological doses of hydrocortisone with no symptoms.

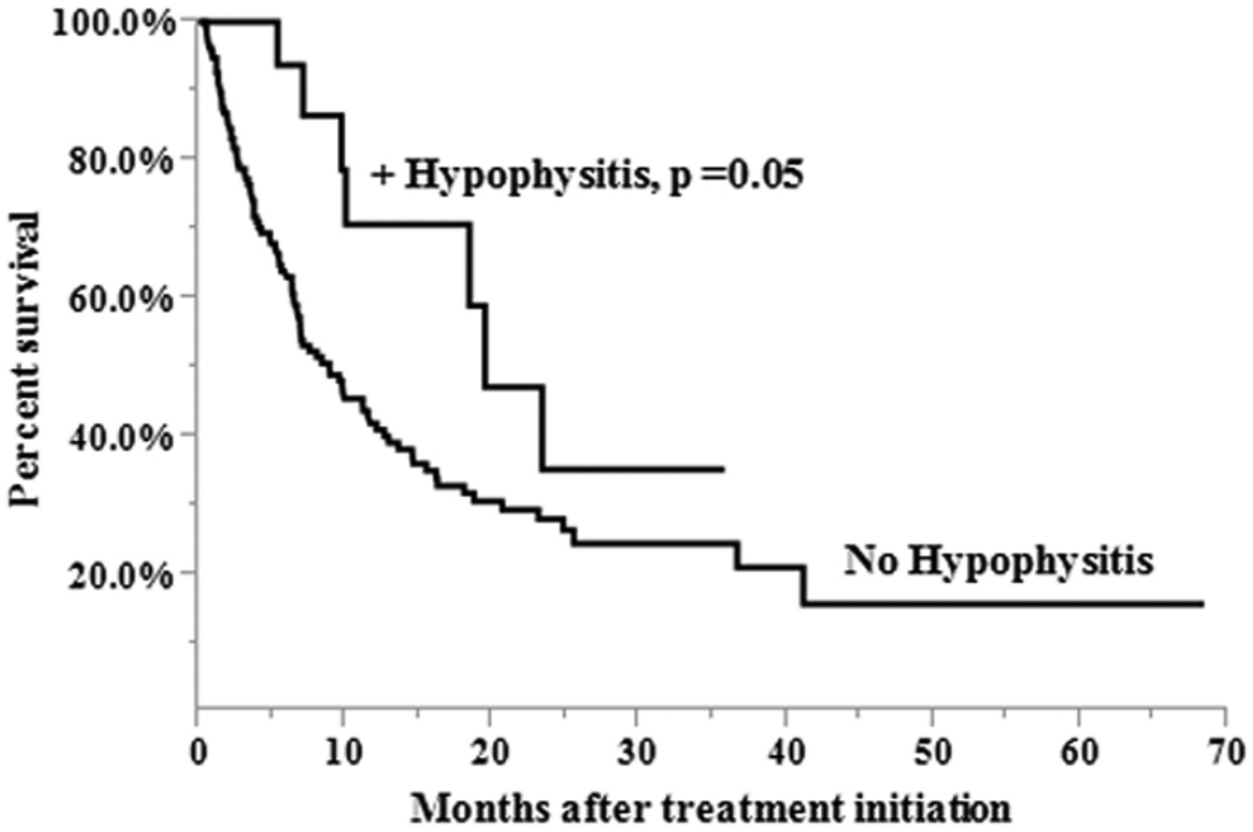
Discussion

- Hypophysitis is being increasingly recognized as an adverse effect of Ipilimumab.
- Ipilimumab is a monoclonal antibody that causes immune mediated destruction of cancerous cells.
- In the treatment of cancer, Ipilimumab can cause an autoimmune flare resulting in endocrinopathies, most commonly hypophysitis.
- Pituitary enlargement as seen on MRI is a specific and sensitive indicator for Ipilimumab induced hypophysitis.
- There should be a high index of suspicion for hypophysitis in patient's being treated with Ipilimumab as if this is left untreated it can be fatal.
- Patients have resolution of their symptoms with discontinuation of the offending agent and hormone replacement.
- MRI abnormality usually resolves after 2 months. However, hormonal recovery is minimal.
- Adrenal insufficiency remains a long-term sequela.

References

1. "Ipilimumab-induced autoimmune hypophysitis: a differential for sellar mass lesions." Rodrigues, B, et. al. JCEM. 2014.
2. "Ipilimumab-Induced Hypophysitis: A Detailed Longitudinal Analysis in a Large Cohort of Patients With Metastatic Melanoma" Faje, A, et. al. JCEM 2014

Kaplan-Meier plots for survival in metastatic melanoma patients, with and without hypophysitis



The Journal of Clinical Endocrinology & Metabolism, Volume 99, Issue 11, 1 November 2014, Pages 4078–4085

Case Presentation 2

- 62-year-old female patient with metastatic non-small lung cancer referred to endocrinology for hyperthyroidism
- She has been receiving nivolumab every 2 weeks
- Thyroid function tests before starting treatment were normal
- Thyroid function test before each cycle were normal till the fourth cycle
- Before the fourth cycle she was found to have low thyroid-stimulating hormone level of 0.03 with elevated free T4 level of 2.2 and elevated level of free T3 of 5.7

Case Presentation 2

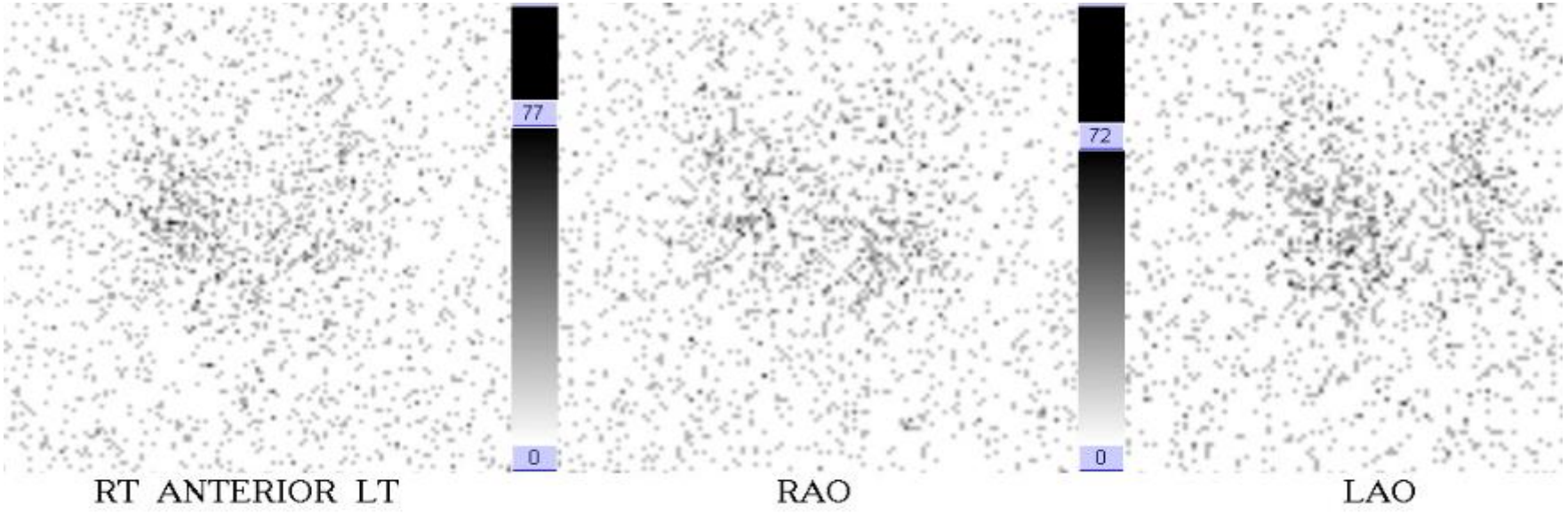
- Patient was complaining of tremors, palpitations, and increased anxiety at time of presentation

- Physical exam was remarkable for tachycardia, heart rate of 120. Thyroid was palpable with no nodules. No bruit or tenderness on physical exam

- Thyroid-stimulating hormone receptor antibody was negative

Case Presentation 2

Thyroid uptake and scan was less than 1%



Case Presentation 2

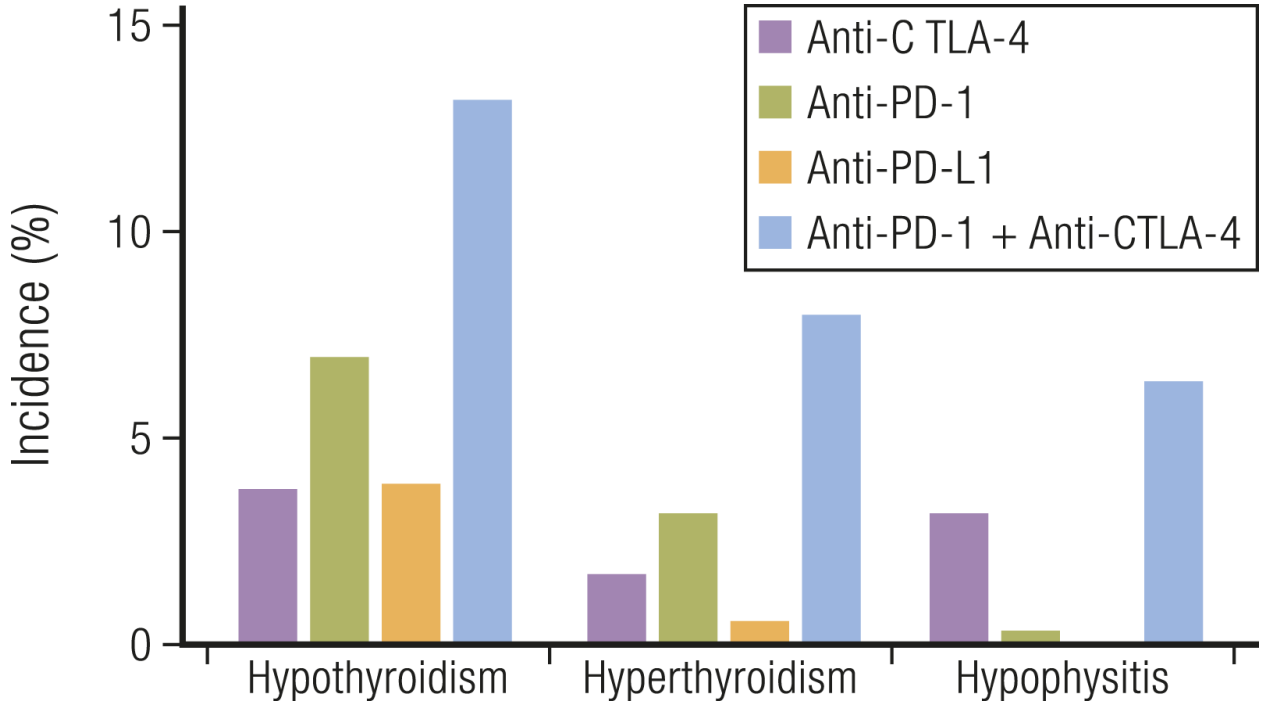
- Immunotherapy-mediated thyroiditis was suspected
- Patient was started on atenolol 50 mg daily for her hyperthyroidism symptoms which was discontinued after few weeks after she was feeling better
- Thyroid function tests few months later were consistent with hypothyroidism and patient was complaining of extreme fatigue
- Thyroid-stimulating hormone level was elevated 22 and a free T4 level was low 0.5
- Thyroid peroxidase antibody was elevated, 210
- Patient was started on levothyroxine 112 µg daily for hypothyroidism for which she has been taking it for 2 years so far

Immune-Related Thyroiditis (irT) with ICP-i Therapy

- Thyroid dysfunction is one of the most common endocrine-related irAEs
- Thyroid dysfunction could be hyperthyroidism, hypothyroidism, and/ or thyroiditis
- Appears to be more common with anti-PD-1 treatment and combination ipilimumab-nivolumab
- Majority of patients develop thyrotoxicosis within weeks after initiation of ICPi then develop hypothyroidism

JAMA Oncol. 2018;4(2):173-182
Thyroid volume 28, Number 10, 2018

Incidence of thyroid dysfunction and hypophysitis induced by different ICPi



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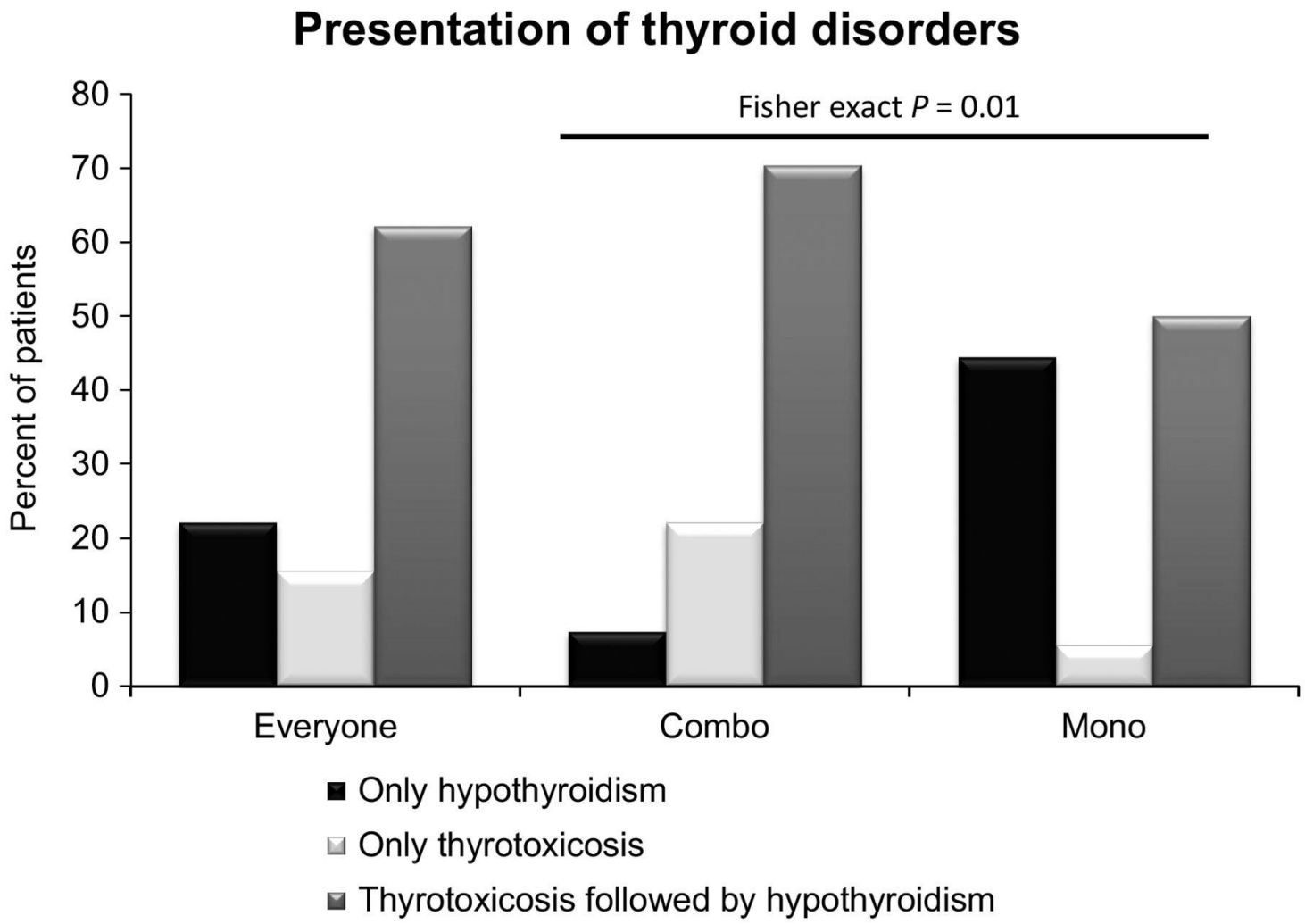
Presentations of thyroid disorders after receiving immune checkpoint inhibition combination therapy or monotherapy.



Hyunju Lee et al. Cancer Immunol Res 2017;5:1133-1140

AACR American Association for Cancer Research
Cancer Immunology Research

Pathophysiology of irT

- Destructive thyroiditis

- Development of positive thyroid autoantibodies like TPO Antibody

In Vivo. 2017;31(5):1035–1039

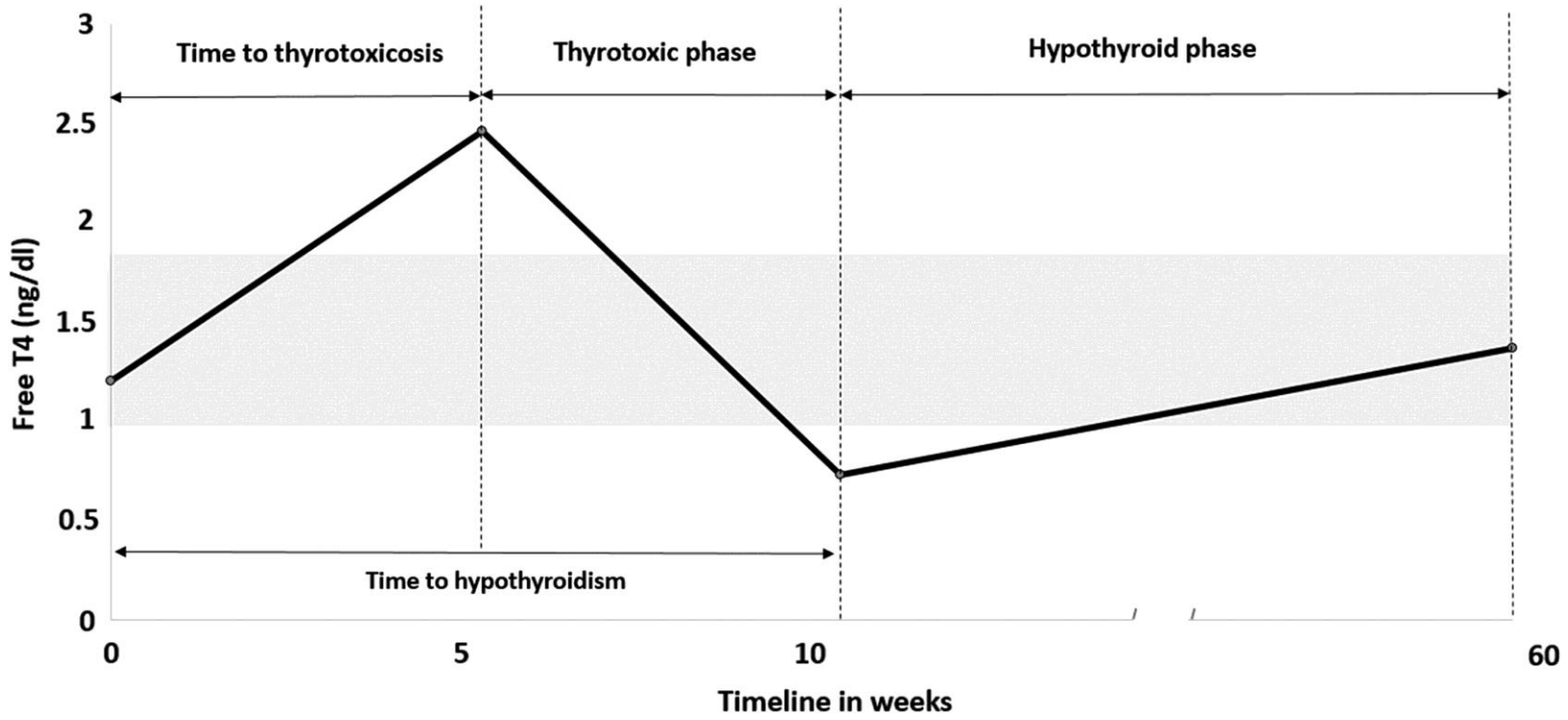
Clinical Course of irT

- Thyrotoxicosis occur mainly due to thyroiditis
- Graves disease has been reported but it’s rare
- irT is characterized by rapid development of asymptomatic thyrotoxicosis followed by a quick transition to hypothyroidism

Case Rep Endocrinol. 2016;2016:2087525

Timeline of Thyroiditis

Thyroid volume 28, Number 10, 2018



Clinical Manifestations of irT

- Thyrotoxicosis symptoms are typically mild and self-limited
- Majority of patients develop permanent hypothyroidism after an average of one month after the thyrotoxicosis phase and 2 months from initiation of ICPi
- It’s very important to differentiate between primary hypothyroidism and secondary hypothyroidism

Diagnostic Workup for irT

- TSH, Free T4, Free T3 levels
- Routine measurement of thyroid antibodies including TPO, TSH receptor Ab, TSI is not recommended
- TSH receptor Ab could be obtained if Graves disease is highly suspected or cause of hyperthyroidism is unclear
- Thyroid imaging is of limited value
- Thyroid uptake and scan could be obtained to evaluate for hyperthyroidism phase if patient did not receive iodine-based contrast for an image for at least 2 months
- Obtaining thyroid ultrasound is usually not helpful

Management of irT

- Beta blockers could be used for hyperthyroidism symptoms
- Anti-thyroid medication is usually not needed unless Graves disease is suspected
- Thyroid hormone replacement for hypothyroidism
- ICPi therapy hold is usually not required
- Close monitoring of thyroid function tests is recommended for patients receiving ICPi therapy

Conclusions

- ICPi are cancer therapies that provide impressive clinical benefit in many advanced malignancies
- It is associated with a variety of irAEs quite different from side effects associated with conventional chemotherapy or radiation treatment
- Immune-related hypophysitis and thyroiditis are most common endocrine irAEs associated with ICPi
- Endocrine irAEs are unique because the manifestations are often irreversible however hormone replacement therapy is effective in most cases
- Oncologists, endocrinologists, emergency medicine physicians, and primary care physicians should be vigilant for these irAEs and coordination of care is very important
- Additional studies are needed to clarify the mechanisms underlying the development of endocrine irAEs and to identify risk factors for irAEs

Questions

Thank You