THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

# "A 65 year old male with fatigue"

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

# Learning Objectives

- Discuss the presentation of subacute adrenal insufficiency
- Discuss the endocrine effects of immune checkpoint therapies

# Initial Presentation

- A 65 year old man presents to endocrinology clinic with severe fatigue for several months duration
- History of a recurrent GEJ adenocarcinoma treated with irinotecan, 5 FU, and nivolumab
- After 6 months of therapy, he developed intractable fatigue

# First visit

## What etiologies are you considering? What would you order?

- Physical Exam

| | |
|---|---|
| BP: | (!) 121/47 |
| Pulse: | (!) 50 |
| Temp: | 36 °C (96.8 °F) |
| TempSrc: | Tympanic |
| Weight: | 75.8 kg (167 lb 3.2 oz) |
| Height: | 175.3 cm (5' 9") |

General- no acute distress

HEENT- normocephalic, moist mucous membranes, pupils equal reactive

Card- RRR, no murmurs

Resp- clear to auscultation bilaterally

Abd- soft, nontender

MSK- no edema, no deformity

Integumentary- tinea versicolor, no increased pigmentation

Neuro- AAOx3, no focal deficit

- ROS

General: fatigue, weight loss, anorexia, decreased activity
HEENT: +visual disturbance increase floaters
Resp: –SOB, - chest tightness
Card: -palpitation, - chest pain, -LE edema
Abd: + abdominal bloating, +diarrhea
GU: -dysuria, -hematuria
End: - heat or cold intolerance, - polyuria, - polydipsia
MSK: + loss of muscle mass
Neuro: +lightheadedness, -syncope

- PMH

HTN
OSA
BPH
GE junction adenocarcinoma (initial surgical resection 2020)

# Laboratory Assessment

| | |
|---|---|
| ACTH 5.0 - 52.0 pg/mL | <3.0 (L) |
| ALDOSTERONE | Rpt |
| Cortisol ug/dL | 0.3 |
| FSH mIU/mL | 28.3 |
| LH mIU/mL | 11.8 |
| RENIN | Rpt |
| Te Binding Globulin 10 - 80 nmol/L | 65 |
| Calculated Free Testosterone pg/mL | 84 |
| Total Testosterone 180 - 800 ng/dL | 395 |
| IGF1 LC MS | Rpt |

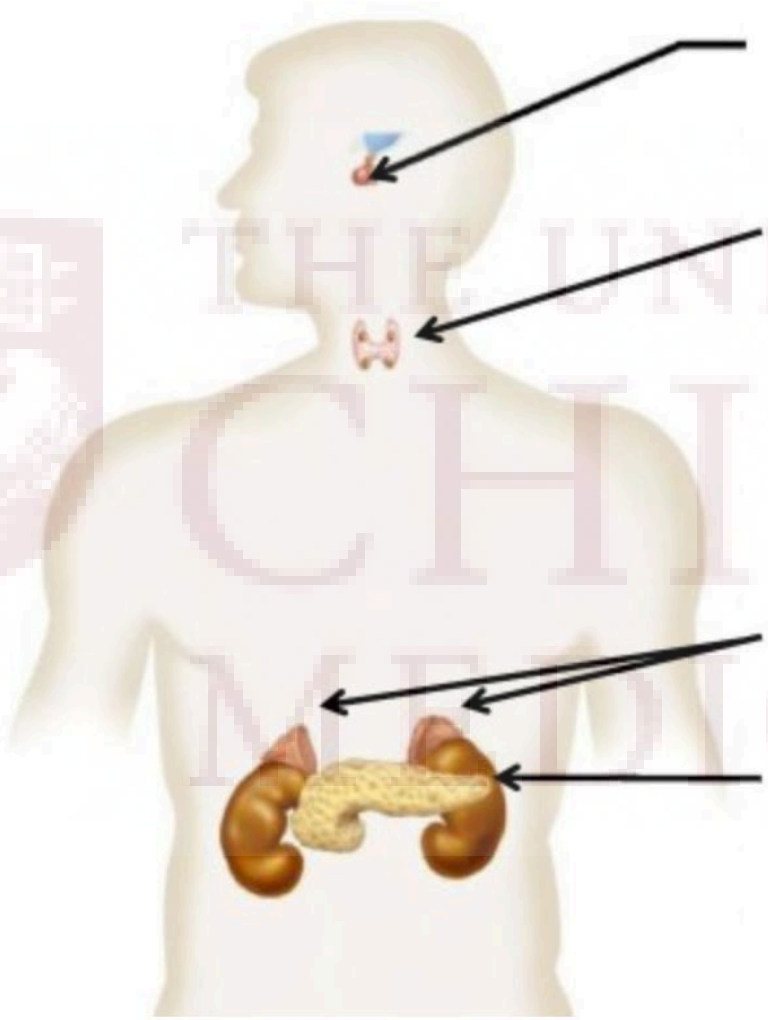
| | |
|---|---|
| Glucose, Ser/Plasma | 73 |
| Sodium | 141 |
| Potassium | 4.8 |
| Chloride | 108 |
| Carbon Dioxide | 23 |
| Anion Gap | 10 |
| BUN | 17 |
| Creatinine | 0.86 |
| eGFR, All | 96 |
| Calcium | 9.2 |

| | |
|---|---|
| Aldosterone <=21 ng/dL | <4.0 |
| Renin ng/mL/h | 1.4 |
| IGF1 LC MS 33 - 220 ng/mL | 86 |
| IGF1 Z SCORE -2.0 - 2.0 SD | -0.67 |
| Triiodothyronine, Free 230 - 420 pg/dL | 242 |
| Thyroxine, Free 0.90 - 1.70 ng/dL | 0.97 |
| Thyroid Stimulating Hormone (TSH) 0.30 - 4.00 uIU/mL | 2.39 |

# Follow Up

- The patient was started on hydrocortisone 20 mg in the morning and 10 mg in the afternoon
- After three days of therapy he reported a return to his baseline, went on a 27 mile bike ride
- Over the course of the ensuing weeks he reduced his dose of hydrocortisone to 10mg in the morning and 5 mg in the afternoon

# Endocrine Effects of Immune Checkpoint Inhibitors (ICIs)



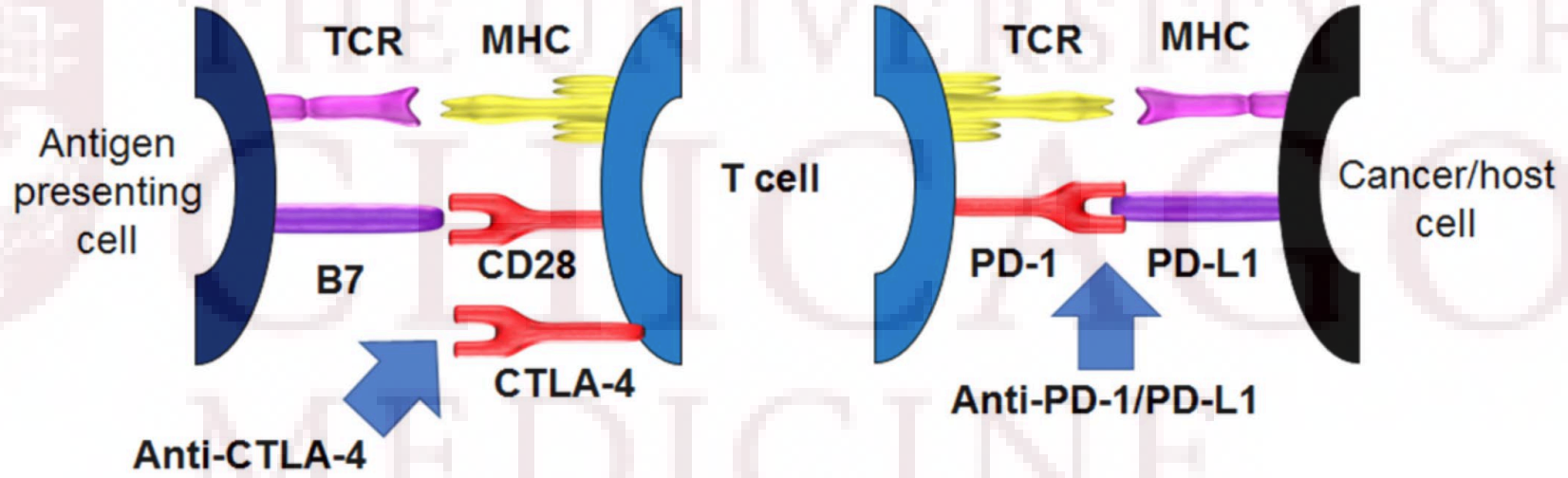
**Pituitary gland**
- Hypophysitis
- Corticotropin (ACTH) decrease
- Secondary adrenal insufficiency[a]

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

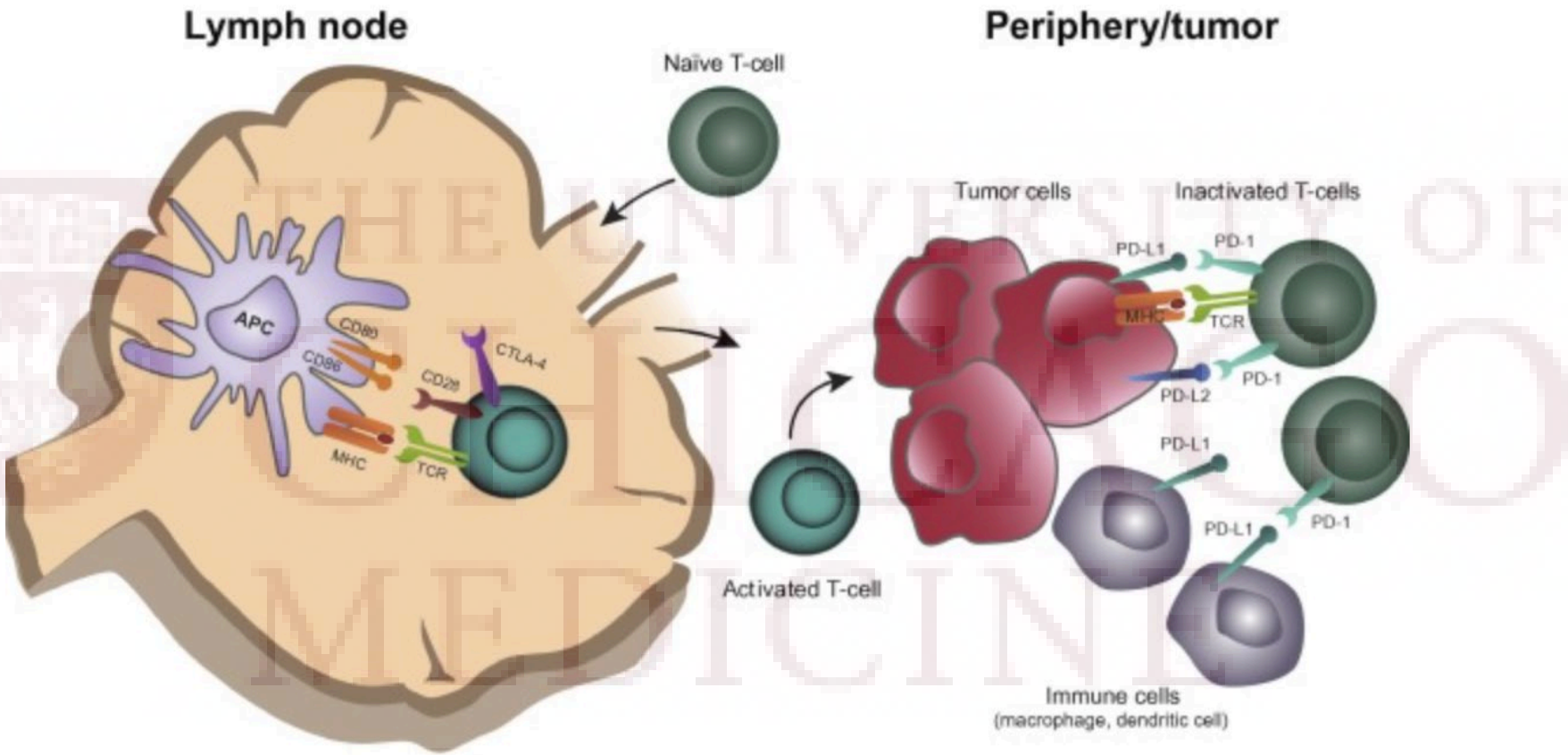
**Adrenal glands**
- Primary adrenal insufficiency[b]

**Pancreas**
- Diabetes mellitus

# Mechanism of Action



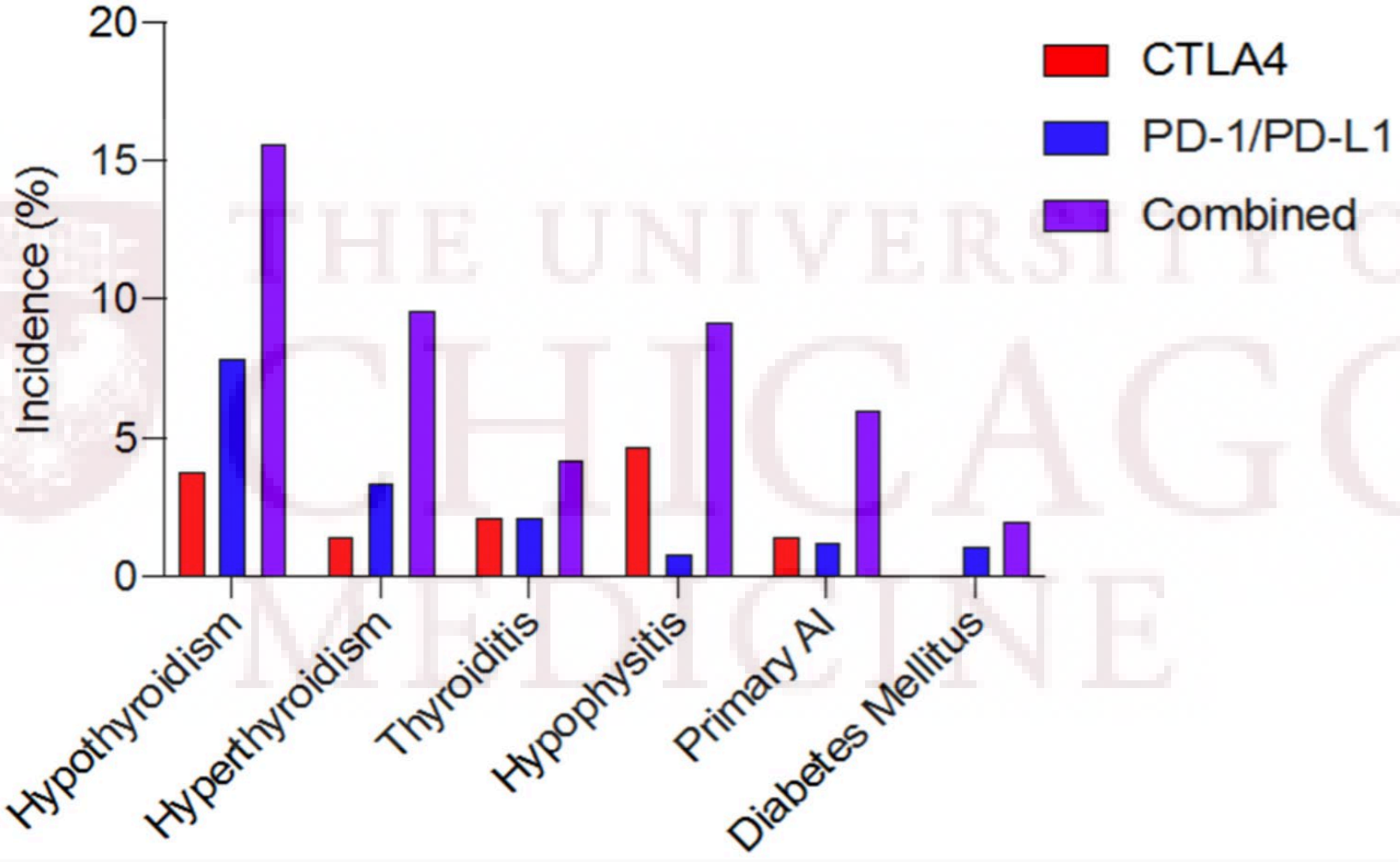
# Mechanism of Action cont'd

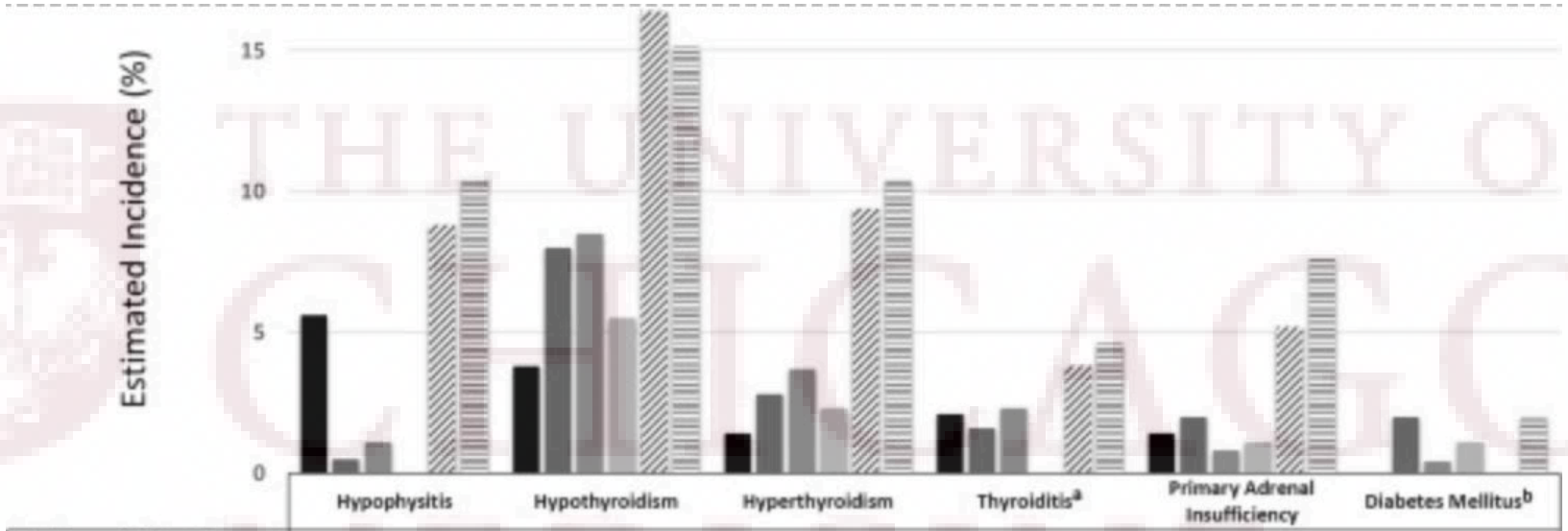


# American Association of Clinical Endocrinology Disease State Clinical Review: Evaluation and Management of Immune Checkpoint Inhibitor-Mediated Endocrinopathies: A Practical Case-Based Clinical Approach

Kevin C.J. Yuen, MD [1] · Susan L. Samson, MD, PhD [2] · Irina Bancos, MD [3] · ... · Sina Jasim, MD, MPH [6] · Leslie A. Fecher, MD [7] · Jeffrey S. Weber, MD, PhD [8] ... Show more

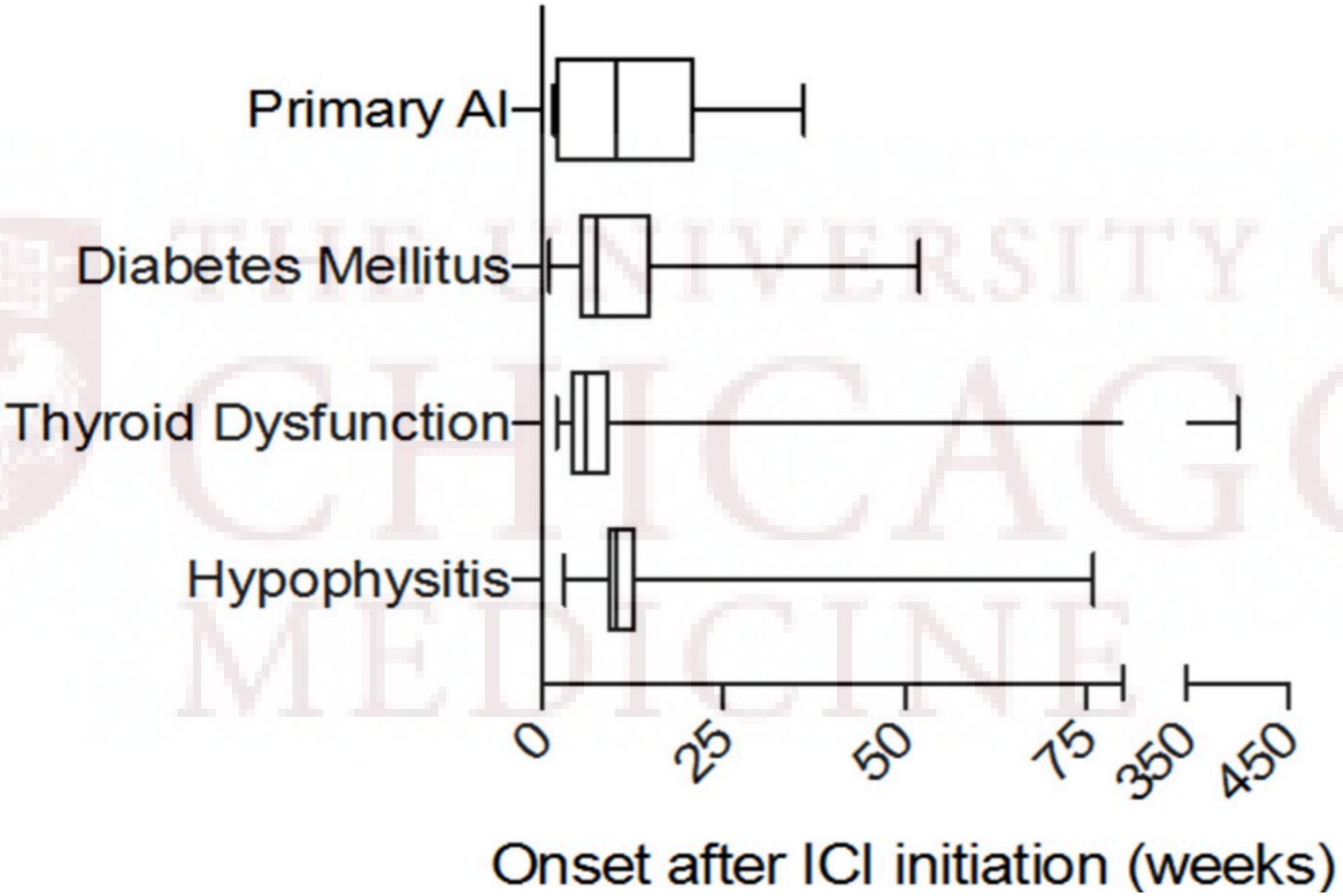
# Frequency of Endocrinopathies






| | Hypophysitis | Hypothyroidism | Hyperthyroidism | Thyroiditis[a] | Primary Adrenal Insufficiency | Diabetes Mellitus[b] |
|---|---|---|---|---|---|---|
| Ipilimumab (CTLA-4) | 5.6 | 3.8 | 1.4 | 2.1 | 1.4 | NR |
| Nivolumab (PD-1) | 0.5 | 8.0 | 2.8 | 1.6 | 2.0 | 2.0 |
| Pembrolizumab (PD-1) | 1.1 | 8.5 | 3.7 | 2.3 | 0.8 | 0.4 |
| Avelumab (PD-L1) | NR | 5.5 | 2.3 | NR | 1.1 | 1.1 |
| Ipilimumab/Nivolumab | 8.8 | 16.4 | 9.4 | 3.8 | 5.2 | NR |
| Ipilimumab/Pembrolizumab | 10.5 | 15.1 | 10.4 | 4.6 | 7.6 | 2.0 |

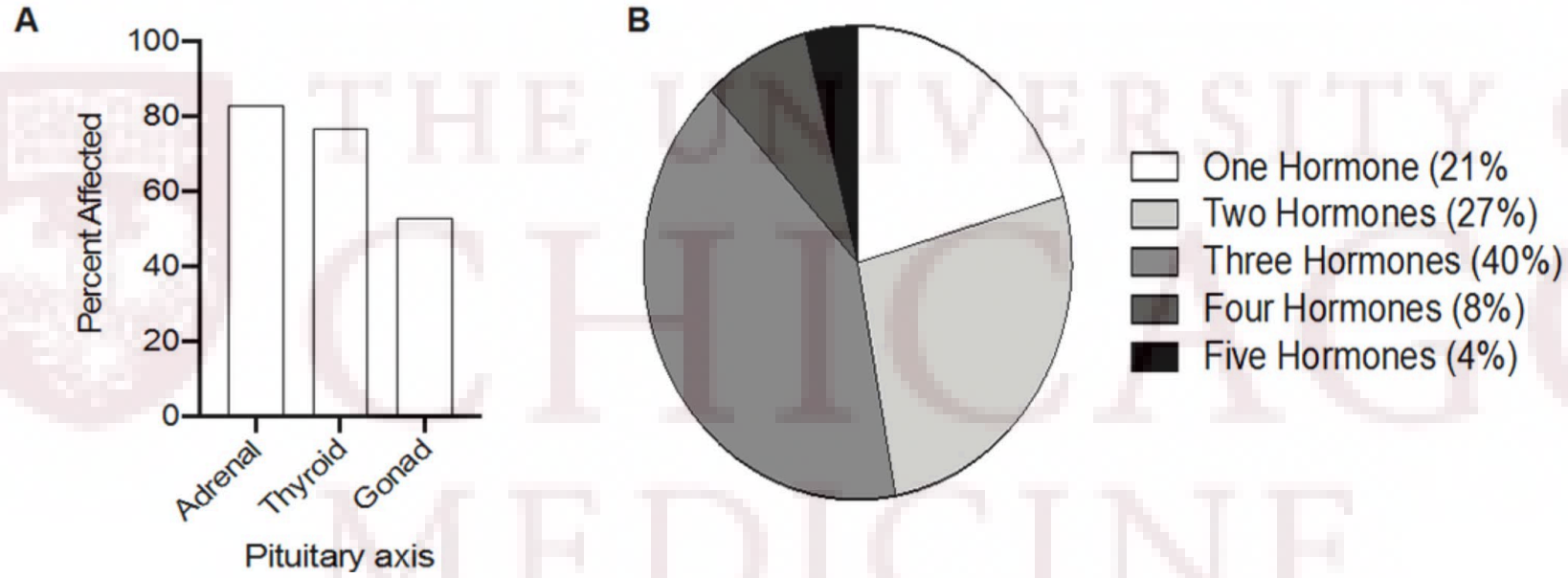
# Onset of Endocrinopathies



# Hypophysitis/Hypopituitarism

- CTLA-4 more often causes hypophysitis with pituitary enlargement and multiple hormones affected. PD-1/PDL-1 more often causes isolated ACTH deficiency
- ACTH deficiency is most common followed by TSH and gonadotropin deficiency
- DI is rare, prolactin levels are variable
- MRI may be indicated in cases of DI or where there are symptoms of mass effect

# Pituitary Axes Affected



# Thyroid Dysfunction

- Thyroiditis (with subclinical or overt hypothyroidism or hyperthyroidism)
- Hypothyroidism
- Thyrotoxicosis
- A common presentation, particularly with anti-PD-1 or anti-PD-L1 monotherapy or combination therapy, is destructive thyroiditis with transient thyrotoxicosis, followed by hypothyroidism, although de novo hypothyroidism and Graves disease have also been reported

# Diabetes Mellitus

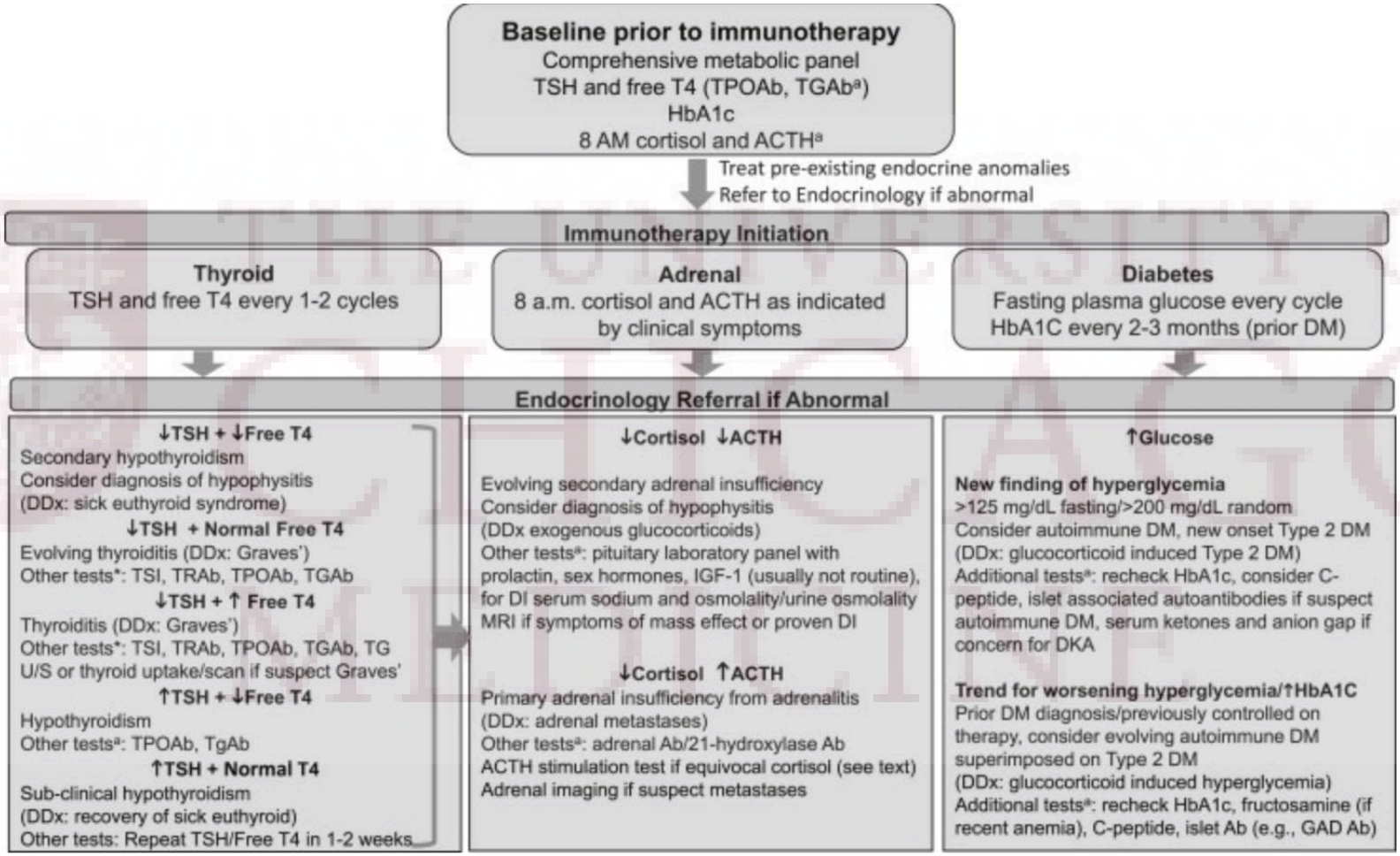
- Most common in PD-1 therapies, occurs in <1% of patients
- Likely genetic predisposition plays a role (HLA genotypes and preexisting pancreatic antibodies are risk factors)
- Highly variable timing of onset (median time to onset ~5 months)

# Adrenalitis

- Primary AI is much less common than secondary. Most often seen with combination therapy
- Primary AI requires mineralocorticoid supplementation, distinguishing from secondary AI can be challenging
- May also indicate a need for imaging to evaluate for adrenal metastases

# Rarer endocrine/metabolic effects

- Hypoparathyroidism
- Cushing disease
- Acquired lipodystrophy
- Elevated lipase, acute pancreatitis → Type 3c diabetes


Baseline prior to immunotherapy
Comprehensive metabolic panel
TSH and free T4 (TPOAb, TGAb[a])
HbA1c
8 AM cortisol and ACTH[a]
Treat pre-existing endocrine anomalies
Refer to Endocrinology if abnormal
Immunotherapy Initiation
Thyroid
TSH and free T4 every 1-2 cycles
Adrenal
8 a.m. cortisol and ACTH as indicated by clinical symptoms
Diabetes
Fasting plasma glucose every cycle
HbA1C every 2-3 months (prior DM)
Endocrinology Referral if Abnormal
↓TSH + ↓Free T4
Secondary hypothyroidism
Consider diagnosis of hypophysitis
(DDx: sick euthyroid syndrome)
↓TSH + Normal Free T4
Evolving thyroiditis (DDx: Graves')
Other tests*: TSI, TRAb, TPOAb, TGAb
↓TSH + ↑ Free T4
Thyroiditis (DDx: Graves')
Other tests*: TSI, TRAb, TPOAb, TGAb, TG
U/S or thyroid uptake/scan if suspect Graves'
↑TSH + ↓Free T4
Hypothyroidism
Other tests[a]: TPOAb, TgAb
↑TSH + Normal T4
Sub-clinical hypothyroidism
(DDx: recovery of sick euthyroid)
Other tests: Repeat TSH/Free T4 in 1-2 weeks
↓Cortisol ↓ACTH
Evolving secondary adrenal insufficiency
Consider diagnosis of hypophysitis
(DDx exogenous glucocorticoids)
Other tests*: pituitary laboratory panel with prolactin, sex hormones, IGF-1 (usually not routine), for DI serum sodium and osmolality/urine osmolality
MRI if symptoms of mass effect or proven DI
↓Cortisol ↑ACTH
Primary adrenal insufficiency from adrenalitis
(DDx: adrenal metastases)
Other tests[a]: adrenal Ab/21-hydroxylase Ab
ACTH stimulation test if equivocal cortisol (see text)
Adrenal imaging if suspect metastases
↑Glucose
New finding of hyperglycemia
>125 mg/dL fasting/>200 mg/dL random
Consider autoimmune DM, new onset Type 2 DM
(DDx: glucocorticoid induced Type 2 DM)
Additional tests[a]: recheck HbA1c, consider C-peptide, islet associated autoantibodies if suspect autoimmune DM, serum ketones and anion gap if concern for DKA
Trend for worsening hyperglycemia/↑HbA1C
Prior DM diagnosis/previously controlled on therapy, consider evolving autoimmune DM superimposed on Type 2 DM
(DDx: glucocorticoid induced hyperglycemia)
Additional tests[a]: recheck HbA1c, fructosamine (if recent anemia), C-peptide, islet Ab (e.g., GAD Ab)

# References


- American Association of Clinical Endocrinology Disease State Clinical Review: Evaluation and Management of Immune Checkpoint Inhibitor-Mediated Endocrinopathies: A Practical Case-Based Clinical Approach Yuen, Kevin C.J. et al. Endocrine Practice , Volume 28, Issue 7, 719 - 731

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# ENDORAMA

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