Cancer Day For Primary Care
Immune checkpoint inhibitors
Endocrine Panel

Medical Oncology: Dr. Joel Gingerich
Endocrinology: Dr. Isanne Schacter
Radiology: Dr. Stephen Ying

10 May 2019

Audience Q/A and feedback: www.sli.do

Presenter Disclosure

- **Faculty / Speaker's name:** Dr. Joel Gingerich

- **Relationships with commercial interests:**
  - **Grants/Research Support:** I participate in industry supported clinical trials at CCMB
  - **Speakers Bureau/Honoraria:** N/A
  - **Consulting Fees:** N/A
  - **Other:** N/A

Mitigating Potential Bias

- All recommendations are supported by evidence and are guideline approved.

Presenter Disclosure

- **Faculty / Speaker's name:** Dr. Isanne Schacter

- **Relationships with commercial interests:**
  - **Grants/Research Support:** N/A
  - **Speakers Bureau/Honoraria:** N/A
  - **Consulting Fees:** N/A
  - **Other:** N/A

Presenter Disclosure

- **Faculty / Speaker's name:** Dr. Stephen Ying

- **Relationships with commercial interests:**
  - **Grants/Research Support:** N/A
  - **Speakers Bureau/Honoraria:** N/A
  - **Consulting Fees:** N/A
  - **Other:** N/A

Learning Objectives

1. Identify common endocrine abnormalities associated with immune checkpoint inhibition
2. Review the work-up and management of suspected endocrine abnormalities associated with immune checkpoint inhibition

Case: 65 year old male

- PMH: Hypertension, Type II diabetes, kidney stones, urinary incontinence (sling procedure), chronic lower back pain
- Meds: Metformin 500mg bid , Irbesartan 75 mg od, Calcium + Vitamin D
- 2008: pT2c, Gleason 4+3 =7 prostate adenocarcinoma, treated with radical prostatectomy.
- 2009: Post-operative rise in PSA → salvage radiotherapy

Case

- 2012: Increasing PSA. CT → Enlarging retroperitoneal lymph nodes consistent with metastatic disease.
  - Medical castration → LHRH agonist
  - PSA decreased. CT → improved RP lymph nodes
  - “Metastatic castration sensitive disease”

- 2015: Increasing PSA.
  - “Metastatic castration resistant disease”
  - Bicalutamide added

Case

- 2016: Increasing PSA. CT → enlarging RP lymph nodes
  - Bicalutamide stopped
  - Enzalutamide initiated

- 2018: Increasing PSA. CT → enlarging RP lymph nodes
  - Enzalutamide stopped
  - Patient enrolled on IND 232 clinical trial (5/2018)
    - Received combination immune-checkpoint inhibition
    - Durvalumab (PD-L1 inhibition)
    - Tremelimumab (CTLA-4 inhibition)

July 2018 (2 months after starting)

- 10 day history of:
- N/V, fatigue, gen. weakness, and diarrhea (2/day)
- Decreased oral intake
- Metoclopramide = minimal benefit
- Spent most of day resting
- Mild improving cough
- (+) sick contact with recent viral-like illness
- No fever, chills, pain, HA’s, or rash

Case

- PE:
  - BP 103/75 mmHg and HR 90/min (sitting)
  - BP 97/69 mmHg and HR 91/min (standing)
  - Respiratory, cardiac, abdominal exam unremarkable

- Labs: CBC, lytes, cr, c-ca normal. AST 44, ALT 36. Chloride 94. C02 21. Glucose 8. PSA ↓

- Bone scan: no evidence of disease
- CT: Improved RP lymph nodes. Hepatic steatosis.

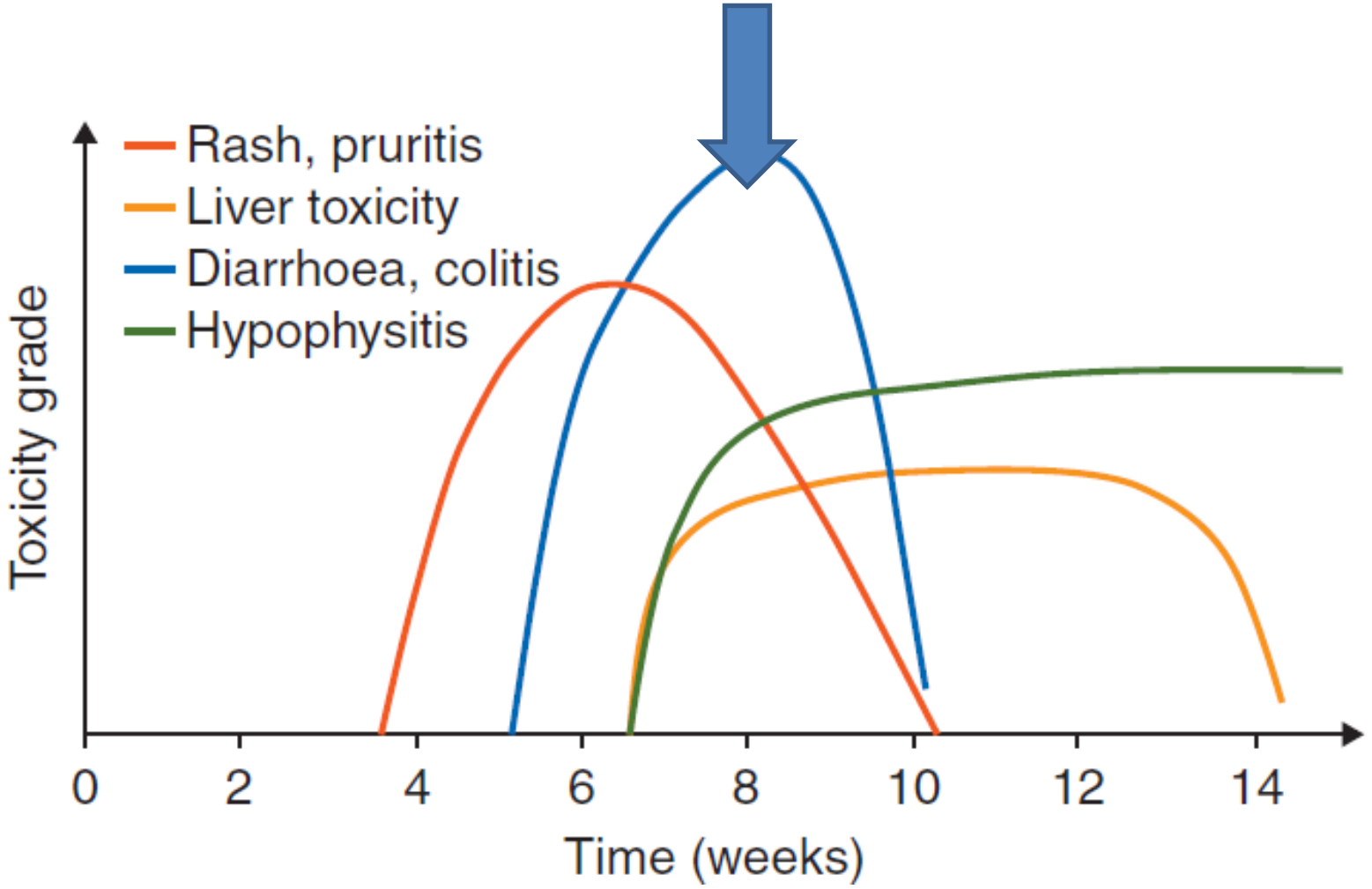
Question 1:

What's your differential diagnosis for weakness, vomiting and diarrhea?

A. Medications: Irbesartan, Metformin
B. irAE endocrinopathy
C. Infectious gastroenteritis
D. irAE enterocolitis
E. All of the above

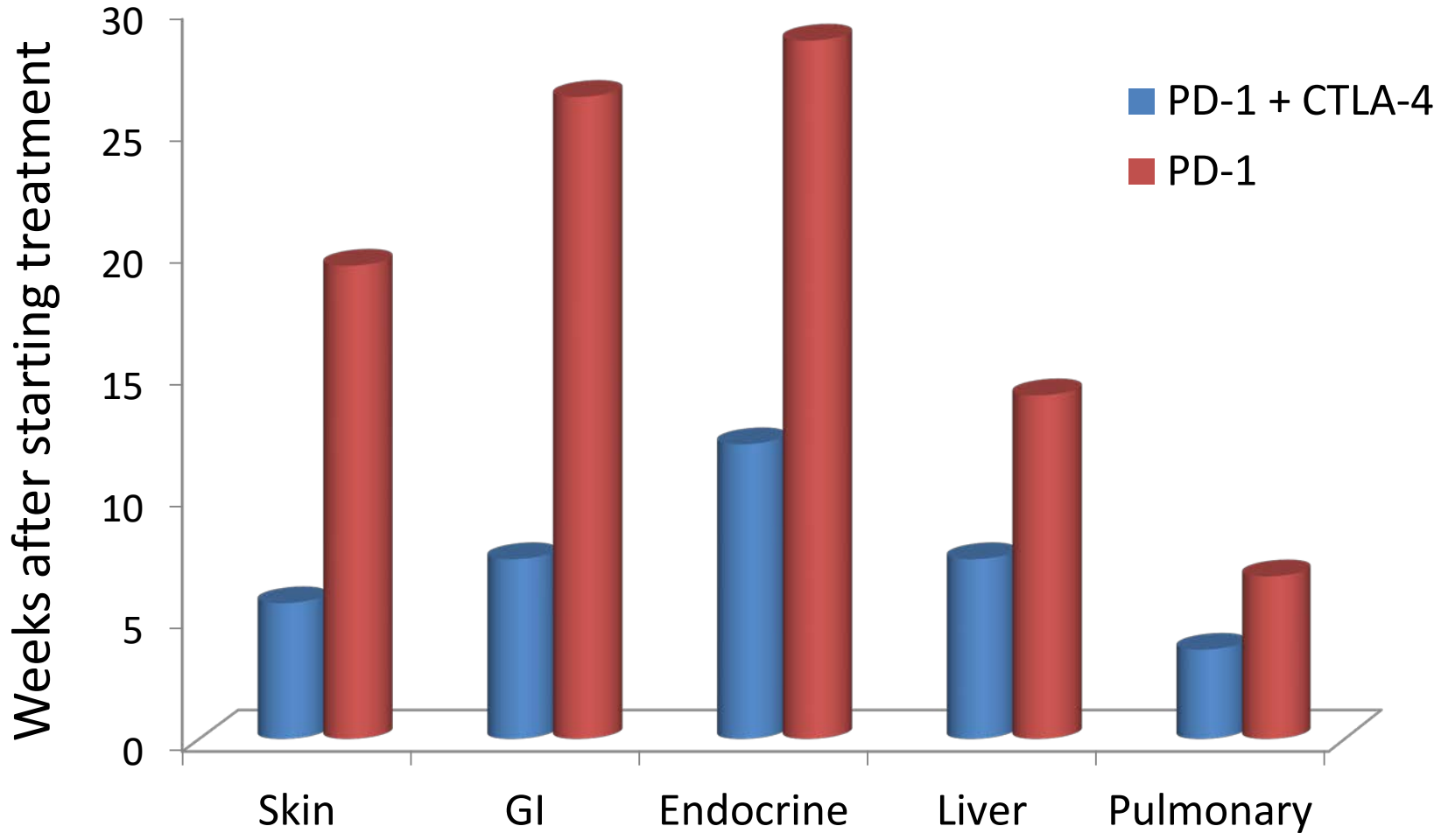
Endocrinopathy and Immuno-oncology

Why do I need to know this?



Weber JS, et al: J Clin Oncol 2012; 30: 2691–2697

Median time to grade 3-4 toxicity: Single agent vs. combination therapy



Larkin J et al. Eur J Cancer 2015; 51 (Suppl 3): S664–S665

Question 2

How often do immune checkpoint inhibitors cause clinically significant endocrinopathies?

A. 3%
B. 10%
C. 20%
D. 40%
E. 60%

Endocrinology: Dr. Isanne Schacter

Signs and Symptoms of Associated Endocrinopathies

- Manifests as feneralized inflammation of the pituitary, thyroid or adrenal glands
  - Non specific symptoms
    - Nausea
    - Headaches
    - Fatigue
    - Visual issues
- Systematic Review (JAMA Oncol 2018)
  - 7551 patients, 38 randomized trials
  - Overall incidence ~10%

Hyperthyroidism

- Incidence ~3.2-8%
- Typical symptoms
- Treat as Graves' disease
  - Check TSH Receptor Antibody
  - Endocrine consult

Hypothyroidism

- Incidence ~3.8-13.2%
- DDx
  - Primary (↑TSH)
  - Secondary (↓/N TSH)
- Management
  - Primary-
    - Treat with weight based (1.6 mcg/kg) dose levothyroxine
  - Secondary:
    - MRI
    - Treat with weight based (1.6 mcg/kg) dose levothyroxine
  - +/- Endocrine consult

Thyroiditis

- Typical triphasic pattern of hyperthyroidism, then hypothyroidism, then eventual return to euthyroidism

- May treat if symptomatic in either phase

Hypophysitis

- Check ACTH/am cortisol, TSH/*f*T4, FSH, LH, estradiol/testosterone, IGF-1, prolactin
- Treat with high dose steroids (1 mg/kg prednisone OD)
  - Reduction of inflammation
- Long term
  - Hydrocortisone 20 mg q am and 10 mg q pm
  - Levothyroxine as indicated

Adrenal Insufficiency

- Incidence ~0.7%
- **Medical Emergency**
  - Patient to proceed directly to urgent care or emergency room
  - Call Endo! We can help
  - **IV** steroids (give dexamethasone if possible if first presentation)
  - Admission to hospital:
    - Steroid conversion/titration
    - Investigations PRN
    - Adrenal insufficiency education
      - Medic alert bracelet, stress dosing, etc.

Type 1 Diabetes Mellitus

- Incidence 0.2%
- Severe hyperglycemia/DKA
- Treat as typical DKA presentation

Endocrine Considerations pre-cycle

- Generally, check TSH, *f*T4, and **am cortisol (if possible)** q 3-4 weeks, before each cycle
  - A **random** cortisol is not necessarily helpful for diagnosis

- Other relevant bloodwork and other investigations will be determined by clinical presentation and overall gestalt
  - i.e. ACTH stimulation test

Ruling in Adrenal Insufficiency

- If am or random cortisol **low (i.e. < 100 nmol/L)**
  - **Presume Adrenal insufficiency**
  - **Treat and consult Endo**

- If cortisol equivocal or overall suspicious → ACTH stimulation test

ACTH stimulation test

- 250 μg cosyntropin (synthetic ACTH) give IV x 1
- Should stimulate adrenal glands to make maximal amount of cortisol (checked at time 0, 30 and 60 min)
  - **Normal response:** cortisol > 550 nmol/L
  - **If < 550 nmol/L → adrenal insufficiency**

- **Dexamethasone interferes least with cortisol assay, so preferred steroid if possible, so that can perform ACTH ASAP (i.e. next day)**

Determining Primary versus Secondary Adrenal Insufficiency

- ACTH stimulation test does not differentiate

- ACTH level (drawn **before steroids given)** can
  - If low, secondary
  - If high, primary

Further reading:

ASCO guidelines:
https://ascopubs.org/doi/full/10.1200/JCO.2017.77.6385

or

ESMO guidelines

https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy

Radiology: Dr. Stephen Ying

Cancer Follow-up Imaging

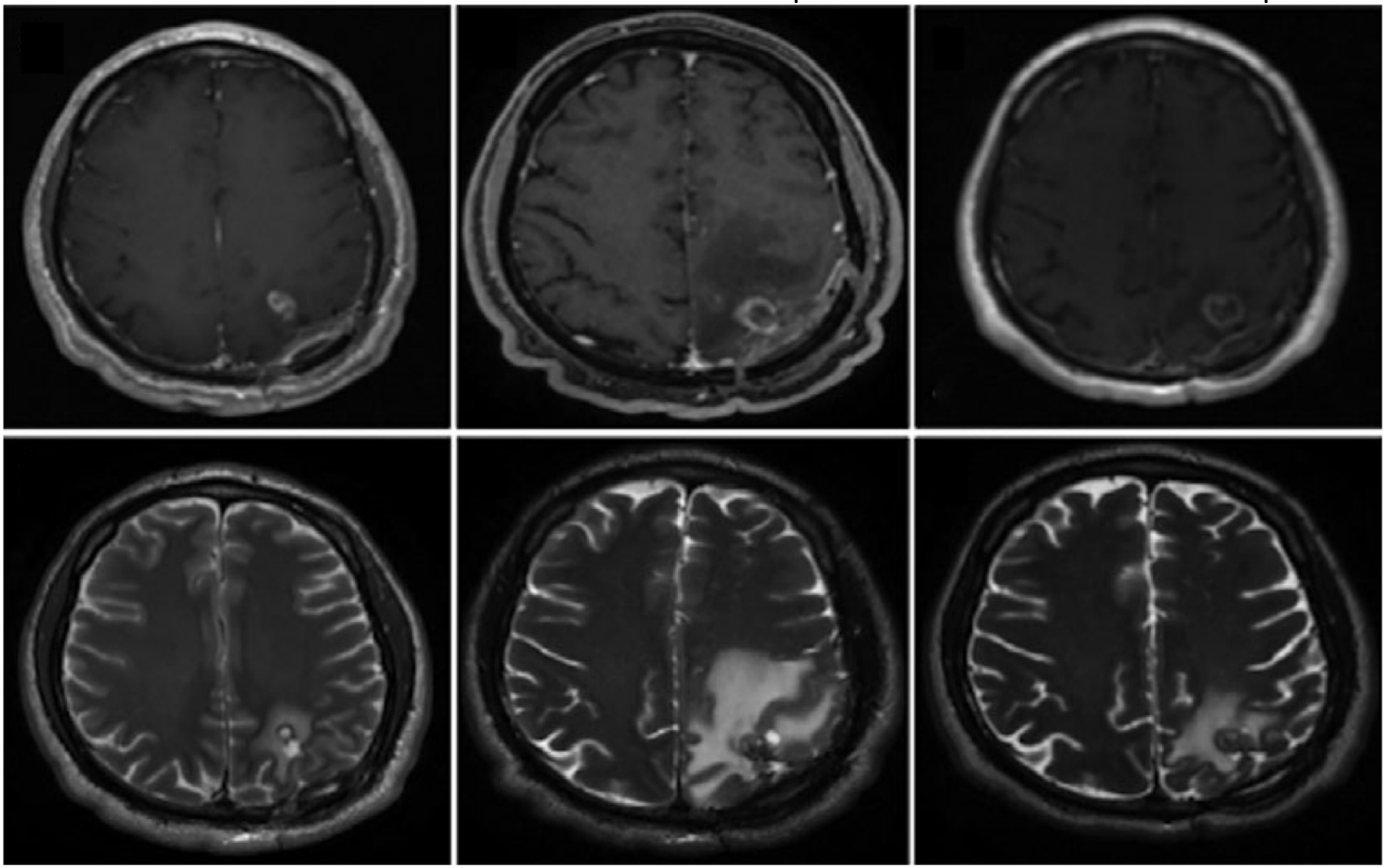
- Traditional cytotoxic chemotherapy and radiotherapy focus on tumor cell death
  - Shrinking tumors or stable disease = success
  - New tumor, tumor growth = treatment failure

- Other findings relate to side effects of treatment
  - Radiation effects on the lung and brain, etc…
  - Side effects of systemic therapy
    - Pulmonary toxicity
    - Hepatic toxicity
    - Enteritis
    - Etc…

Cancer Follow-up Imaging

- Treatment with immunomodulators can have a varied response to treatment
  1. Decrease in size (traditional desired response)
  2. Stable disease
     - Often followed by eventual decline in disease
     - Thought to be delay from activation of immune system
  3. Delayed tumor response after initial increase in tumor
     - Tumor growth during delay in immune activation and/or cell infiltration of tumor
  4. New lesions
     - Appearance of new lesions prior to decrease of tumor burden
     - Type 3 response to micrometastases

Thoracic Cancer **9** (2018) 1770–1773



Pseudoprogression in lung cancer metastasis

Cancer Follow-up imaging

- Immunotherapy-specific adverse reactions
  - Colitis
  - Hepatitis
  - Hypophysitis
  - Thyroiditis
  - Myositis
  - Arthritis
  - Sarcoid-like reaction
  - Etc…

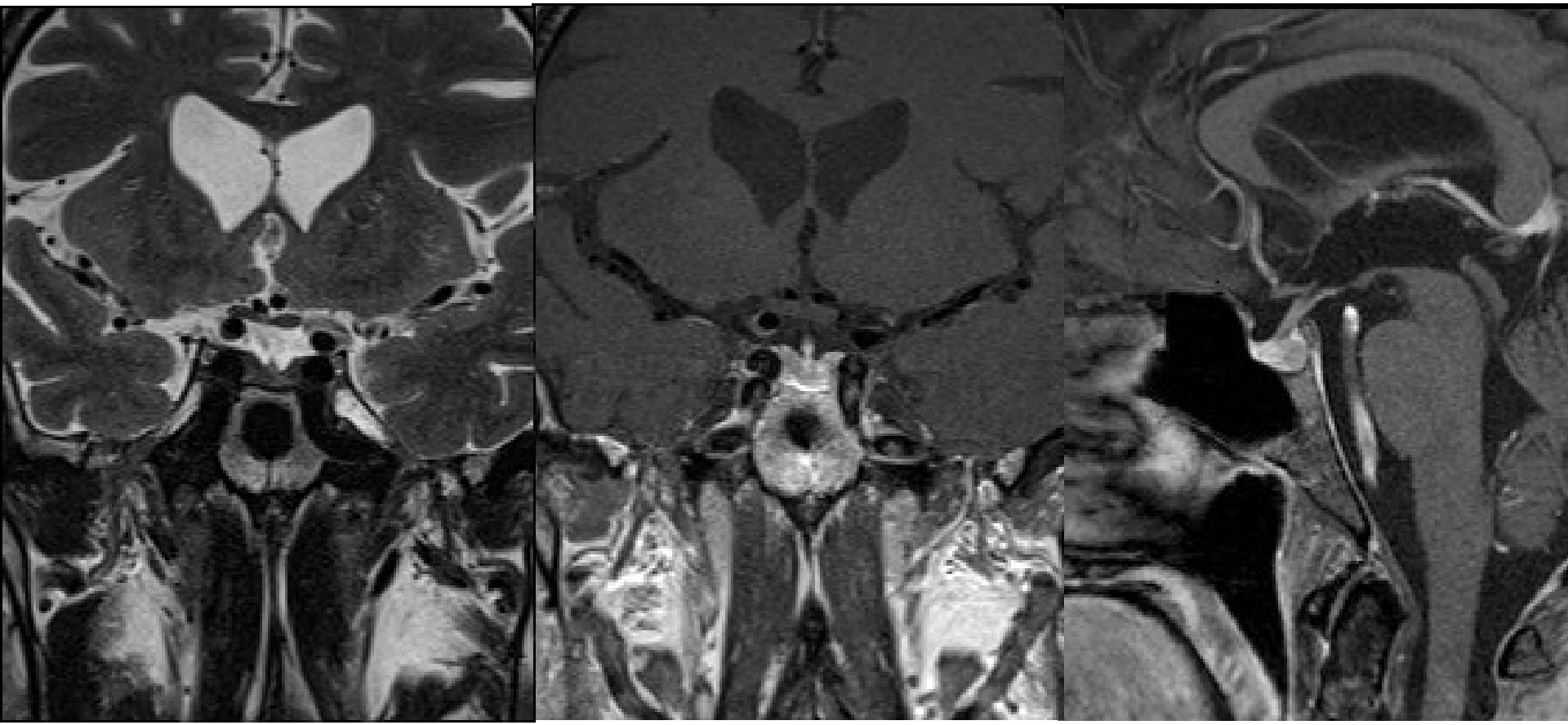
History is important for accurate interpretation of imaging follow-up

- Date/location of prior imaging
- Timing of the scan relative to start of treatment

On ordering imaging

- Relevant **history** and clinical **question**
- A subspecialty radiologist is available during all regular working hours for consultation
  - Call the department (MR, CT)
- If a scan is needed in <1wk, it is best to call the radiology department
  - Bypass “central intake”
  - Radiologist to confirm acuity/timeline and protocol
- Otherwise, the history should be able to determine scan priority

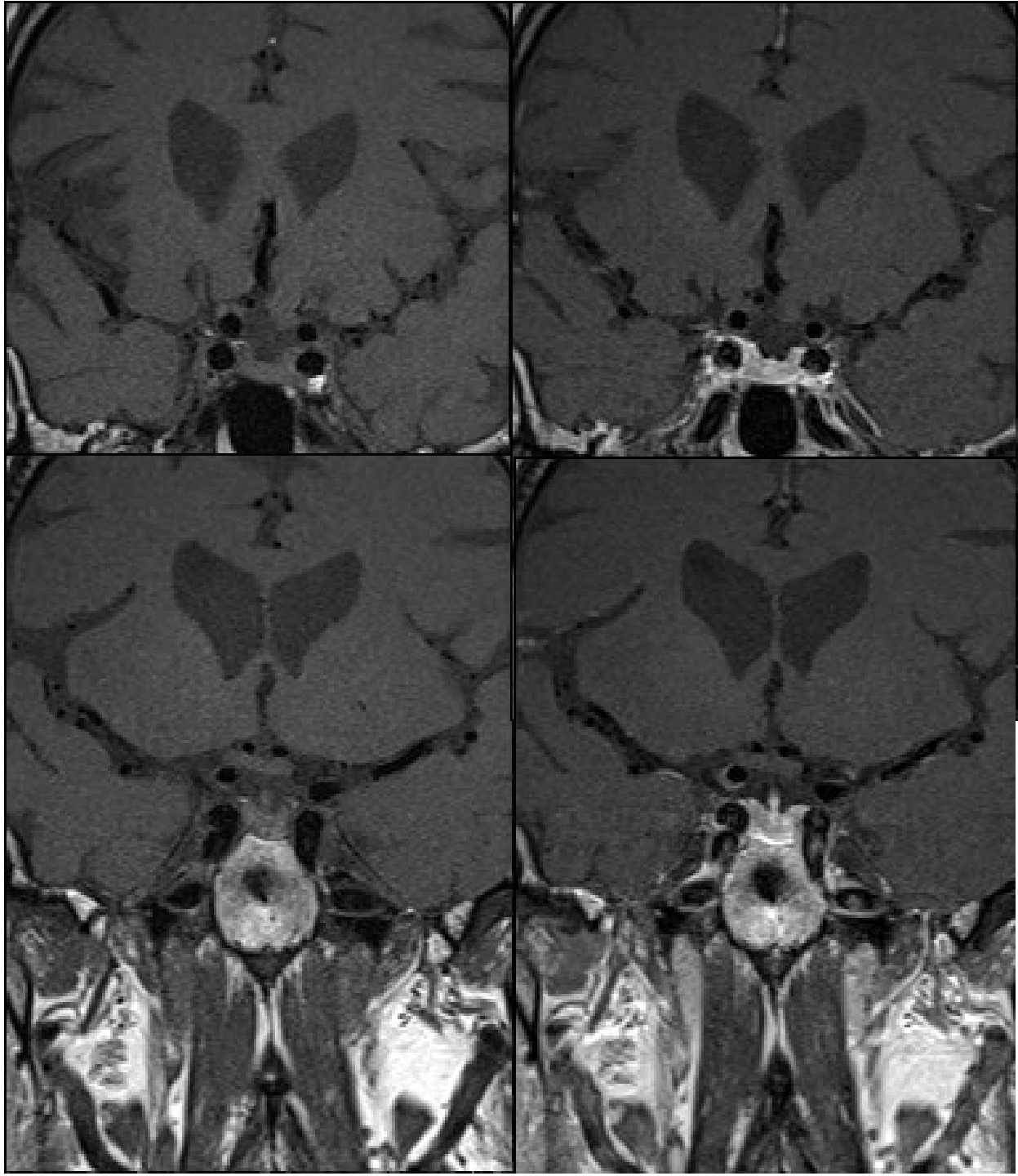
Our Case



Our case

- No prior neuroimaging
- Clinical Hx: “I strongly suspect autoimmune hypophysitis”

- Relatively normal pituitary volume
- Mild heterogeneity, minor asymmetry



Normal pituitary imaging anatomy

- Pituitary volume changes with age and hormonal status
  - Puberty/pregnant patients have the largest glands
  - Younger>older patients

- Max height
  - Adult male approx. 8mm
  - Adult female approx. 9mm
  - Pregnancy 12mm

- Pituitary stalk <2-3mm

- Enhances avidly with Gadolinium contrast
  - Portal circulation system

What's going on?

- Autoimmune hypophysitis usually has mild to moderate diffuse enlargement of the gland
  - Must distinguish GROSS from RELATIVE enlargement
  - Relative enlargement may only be seen in prior, or serial imaging
- Rarely, the pituitary may have a normal appearance
- A normal pituitary does not exclude hypophysitis
- Ddx of pituitary enlargement:
  - Physiologic
  - Tumor
    - Metastasis, adenoma, craniopharyngioma
  - Infiltrate:
    - Lymphocytic, IgG-4, granulomatous, Langerhans

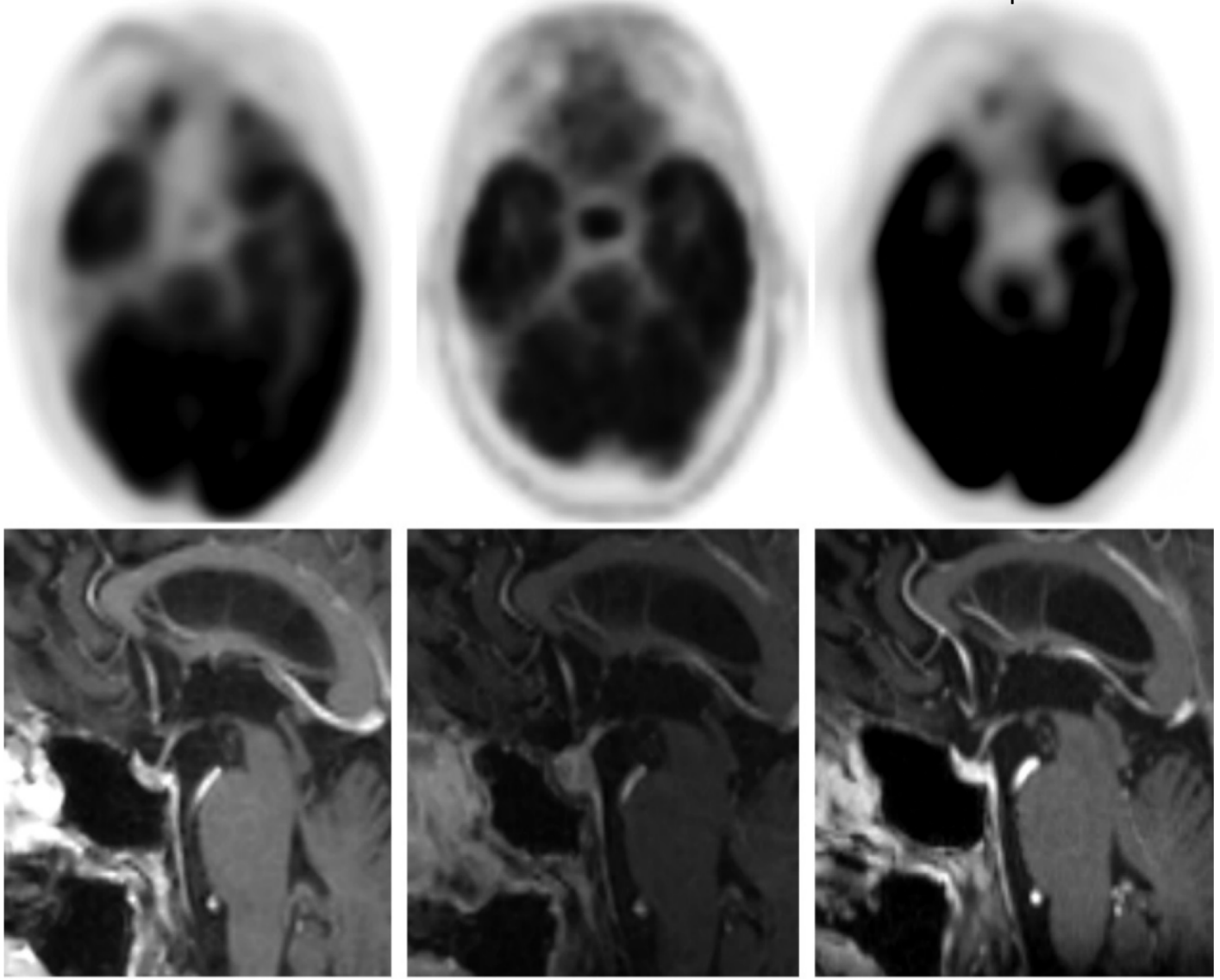
RadioGraphics 2015 35:2, 424-437

Hypophysitis

PRE

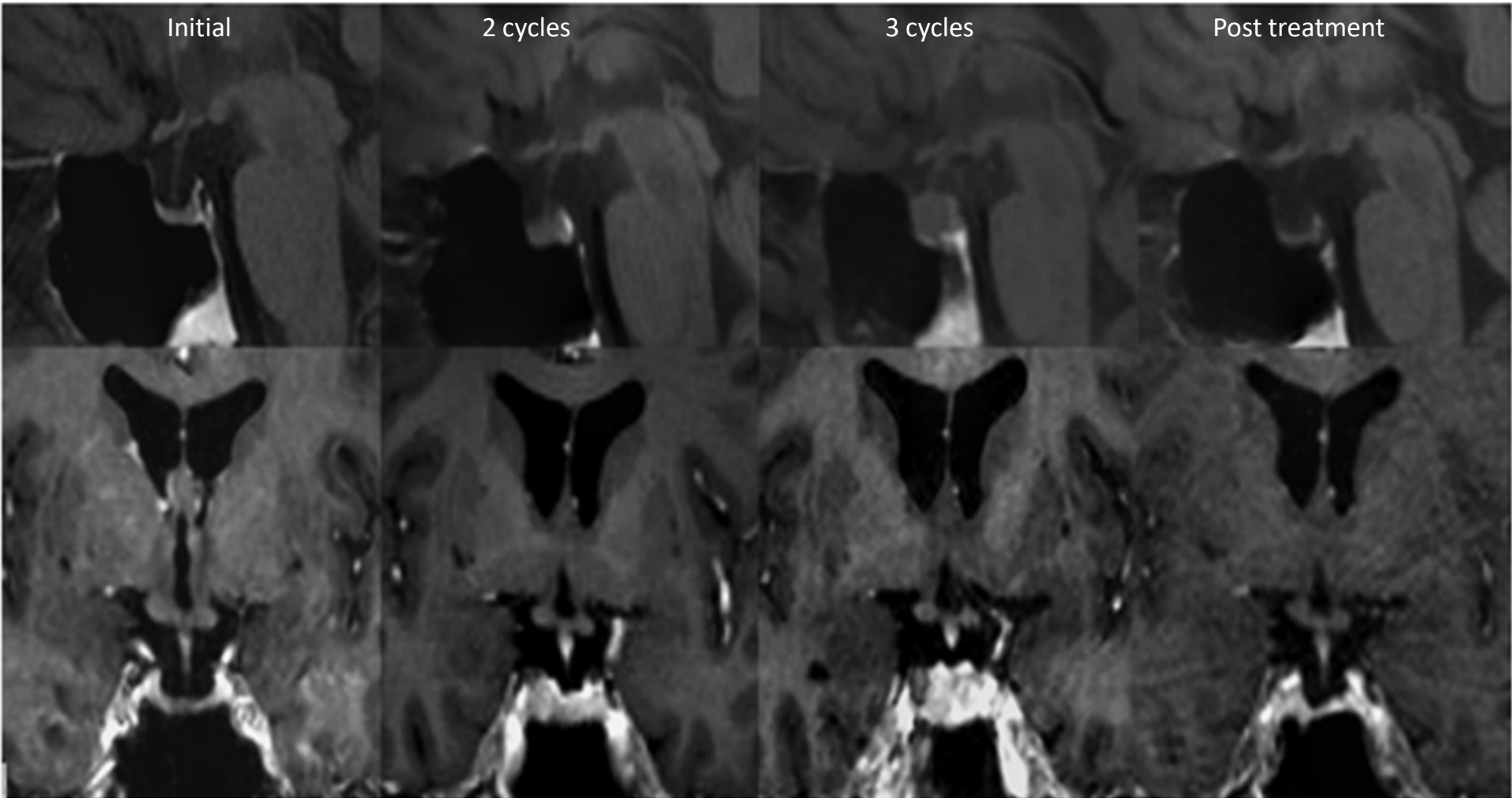
1 Month Post

2 Months post Treatment

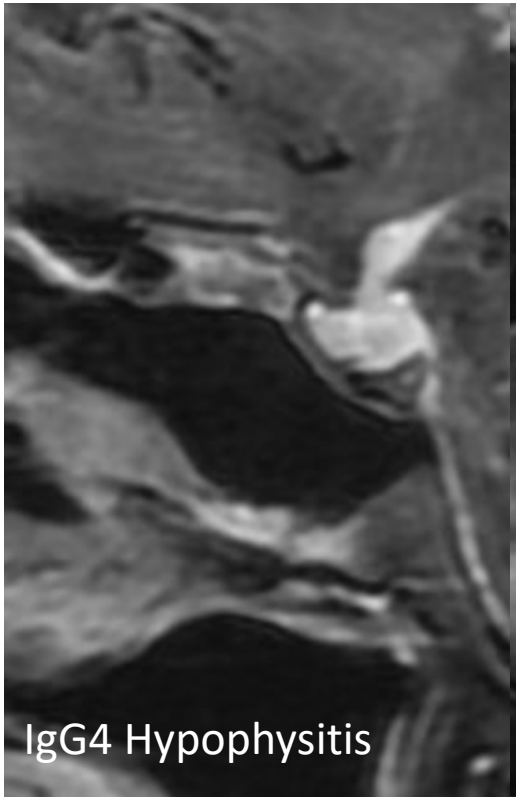


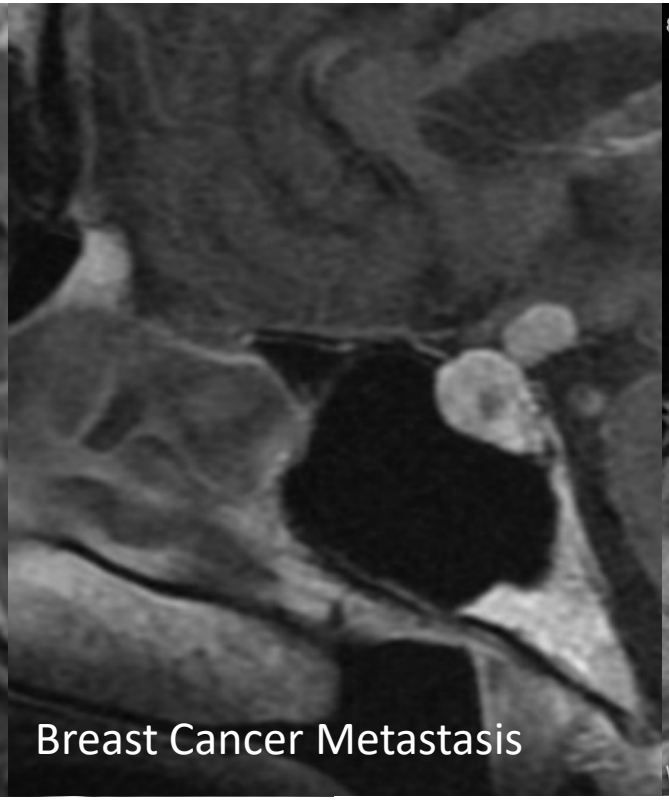
J Clin Endocrinol Metab, November 2014, 99(11):4078–4085

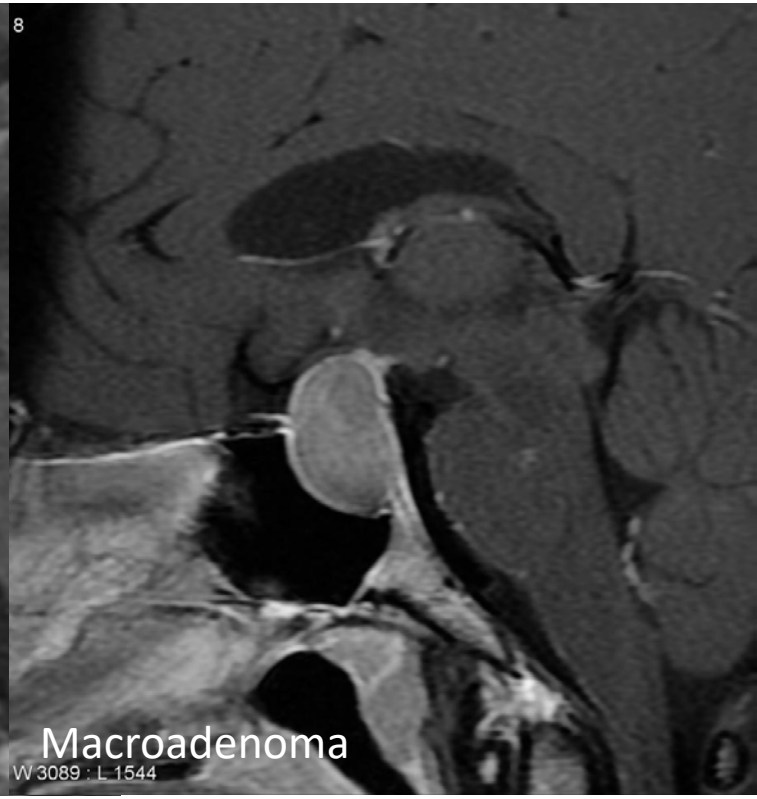
Hypophysitis



Other things to consider





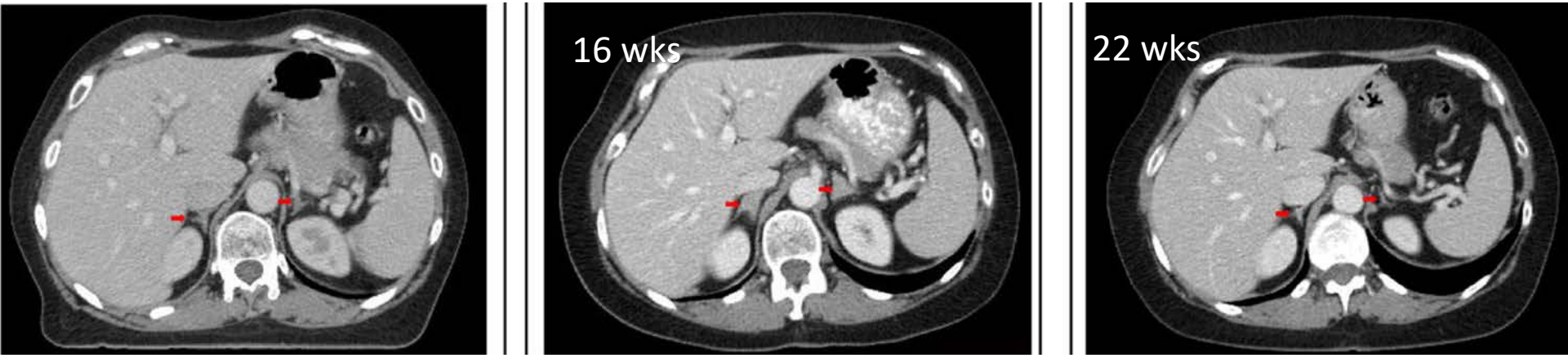


IgG4 hypophysitis case courtesy of Dr Rebecca Dumont Walter, Radiopaedia.org, rID: 42897
Breast Cancer case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 44692
Macroadenoma case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 5277

Lancet Diabetes Endocrinol. 2013 November ; 1(3): e15.

Adrenalitis

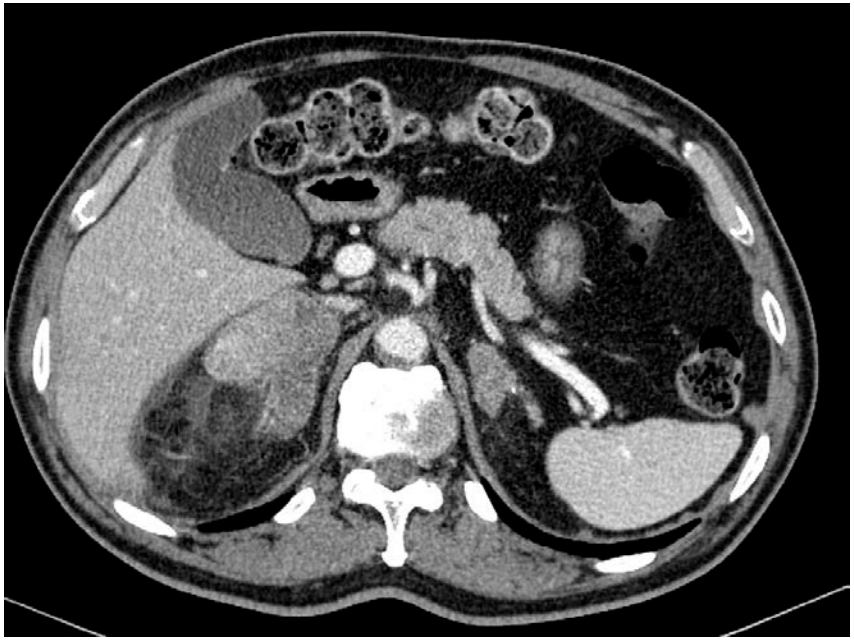
- Dynamic size change in adrenal glands
  - Can be subtle
  - Smooth enlargement
- Clinically evident when insufficiency develops



Other things to consider

Adrenal metastasis

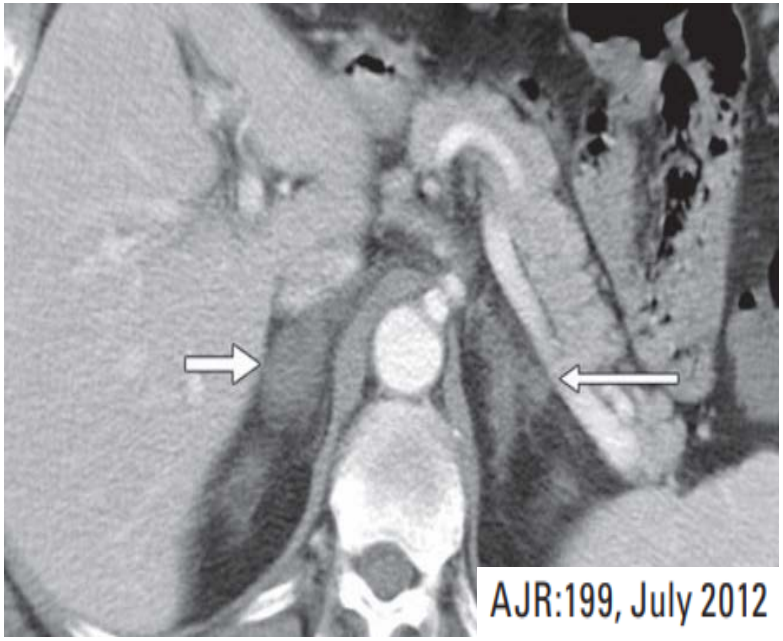
- Focal/nodular
- Unilateral mass



Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 31602

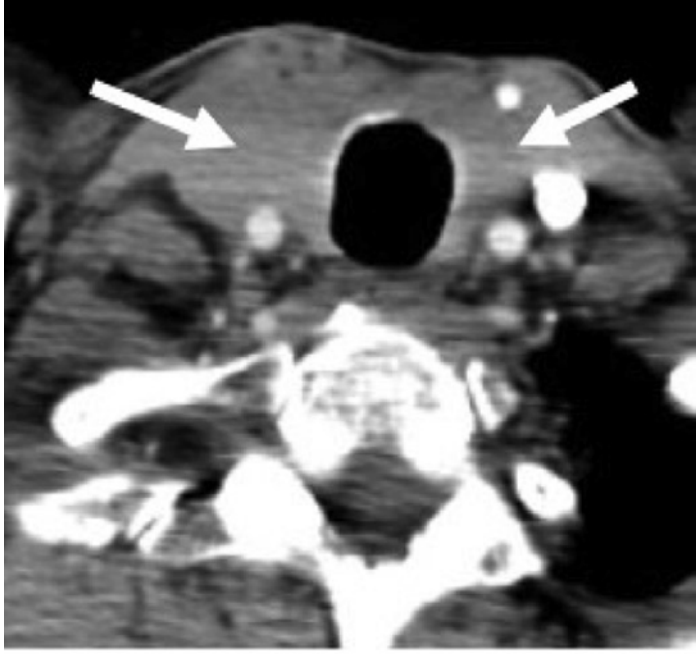
Hemorrhage

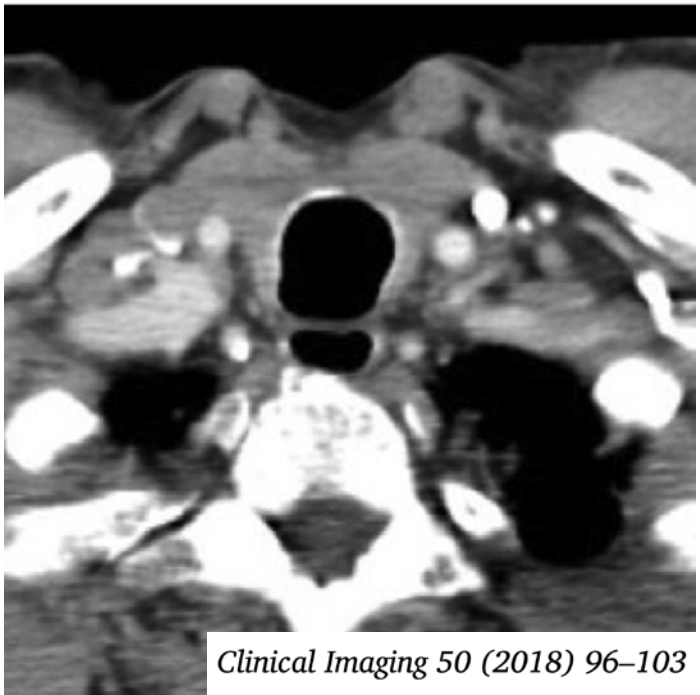
- Blood attenuation
- Resolves over time



Thyroiditis

- Can present as hyper or hypothyroid
- Thyroid can be enlarged and hypoenhancing in inflammatory phase, atretic afterwards





Clinical Imaging 50 (2018) 96–103

Medical Oncology: Dr. Joel Gingerich

Back to our case

- Given the marked weakness, decline in performance status, lack of other obvious causes: suspicion for irAE endocrinopathy.

- Patient received 2L of NS with improvement in symptoms.

Test results

- Random serum cortisol obtained early afternoon: **32 nmol/L**(normal level in am: 140-690 and pm 80-440)
- TSH: 0.2 (low), Free T4: 18.1 (normal)
- Testosterone: < 0.01 Note: patient on androgen deprivation therapy
- Serum ACTH: Pending

Question 3

What do you do next?

A. Await ACTH results
B. Findings consistent with adrenal insufficiency = start steroids
C. Repeat serum cortisol (morning blood draw)
D. Order a ACTH stimulation test

Additional results + Question 4

- ACTH stimulation test:
  - serum cortisol: 23 (AM), 152 (30 min), 224.5 (60 min)

- Serum ACTH: 0.5 (**low**)

- **Are the findings consistent with:**

  A. Primary adrenal insufficiency

  B. Secondary adrenal insufficiency (hypophysitis)

  C. Subclinical adrenal insufficiency

Back to our case

- Started on Dexamethasone 2mg daily
- Seen by endocrinology, steroid changed to Hydrocortisone 10 mg am and 5 mg pm.
- MRI brain was performed to rule out optic chiasma compression.
- Immune checkpoint therapy was continued.

Question 5

	July 18	August 18	September 18
T4	18.1	30.3	52
TSH	0.2	<0.015	<0.015
TSH Receptor Ab			<0.1

What diagnosis explains the thyroid function tests in September 2018?

A. irAE Hypophysitis
B. irAE Graves disease
C. irAE Thyroiditis
D. A & C
E. A & B

Back to our case

- The patient was diagnosed with thyroiditis
- He required a short course of Thiamazole
- His TSH and Free T4 normalized

- The patient has continued on the clinical trial, feels well, remains active and has not had further immune related toxicity.
- He has an ongoing response ~ 1 year after starting treatment

Questions