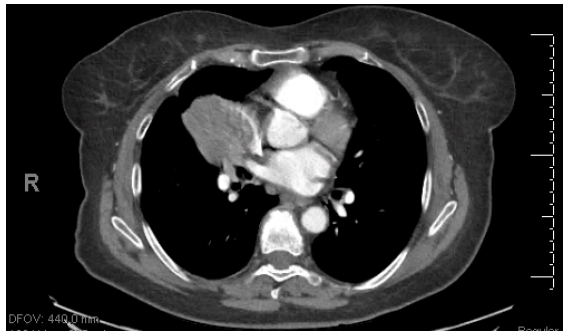
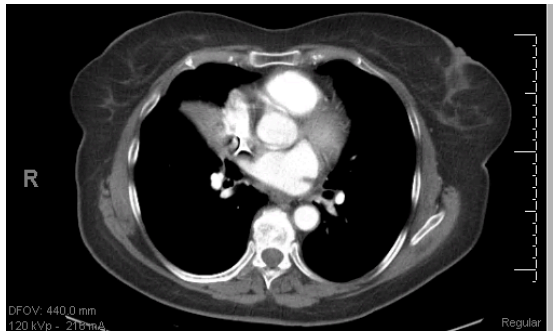
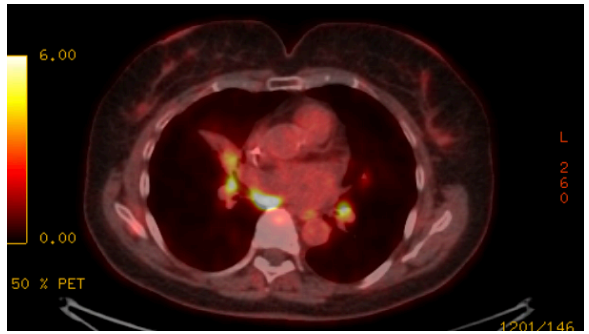
Case Study #1

- 69 woman with history of Type I DM and light smoking history presents with lung mass, pleural effusion and bony lesion. Biopsy demonstrates metastatic lung adenocarcinoma.
- Molecular profiling demonstrates KRAS G12C mutation, along with STK11, and ATM mutations. PD-L1 is 0%.
- She is started on therapy with carboplatin/pemetrexed + pembrolizumab.

- Scans after two cycles demonstrate decrease in the primary but mild increase in hilar adenopathy. Subsequent scans consistent with overall stable disease, with ongoing response in primary and increase in LN size and FDG avidity.







- Cr increased from 1.0 -> 1.3 -> 1.52 -> 1.75
- Kidney biopsy and EBUS demonstrates non-caseating granulomas consistent with sarcoid-like reaction to ICI
- ICI held and pt started on steroids with imrpvement in Cr

Case Study #2

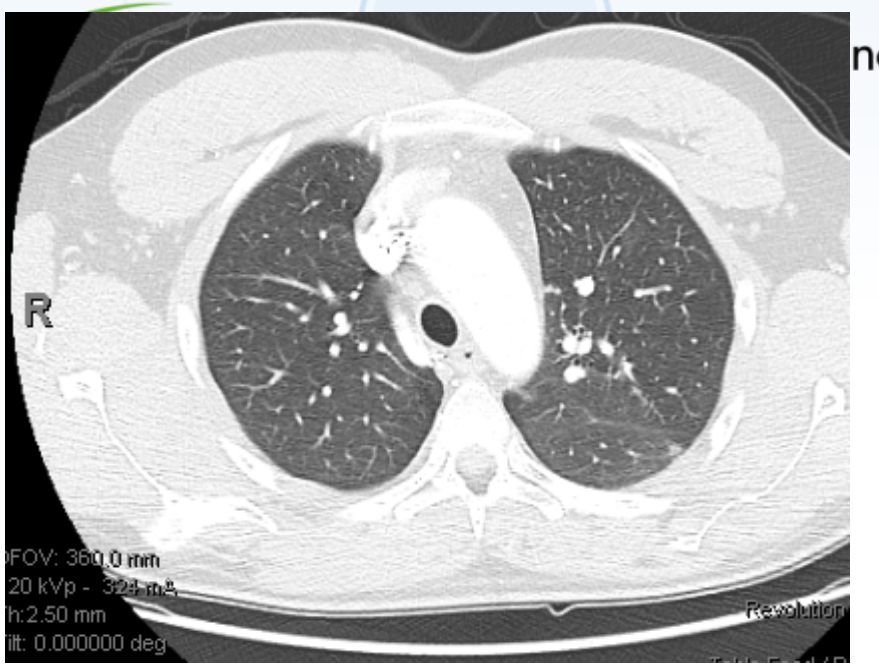
- 68 year old woman w/ RCC
- Treated with PD-1 blocker
- Three months into therapy presents with swelling in the joints of her hands
- ESR and c-reactive protein are elevated

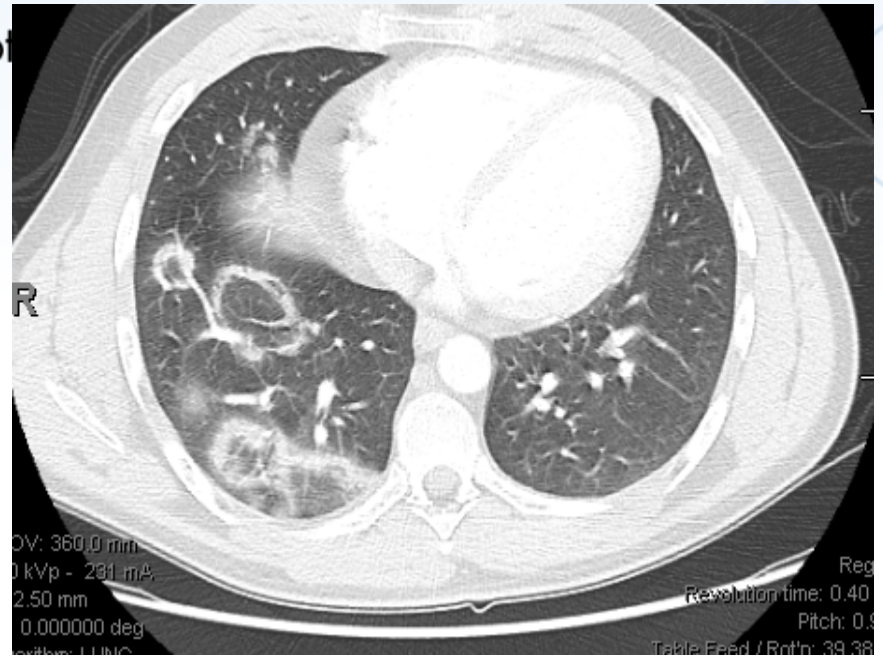
- ICI therapy temporarily stopped
- Patient was started on prednisone 60mg and referred to rheumatology
- Rheumatologist diagnosed inflammatory arthritis, reduced prednisone to 20mg a day with taper to <10mg a day over three weeks
- Patient unable to tolerate taper and was placed on methotrexate 15mg a week
- Patient improved, ICI resumed

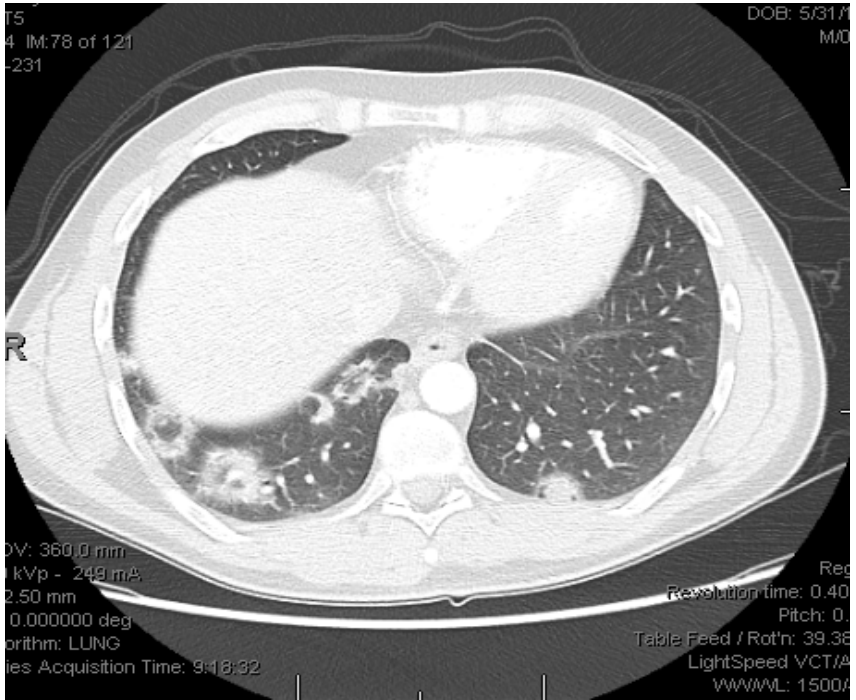
Case Study #3

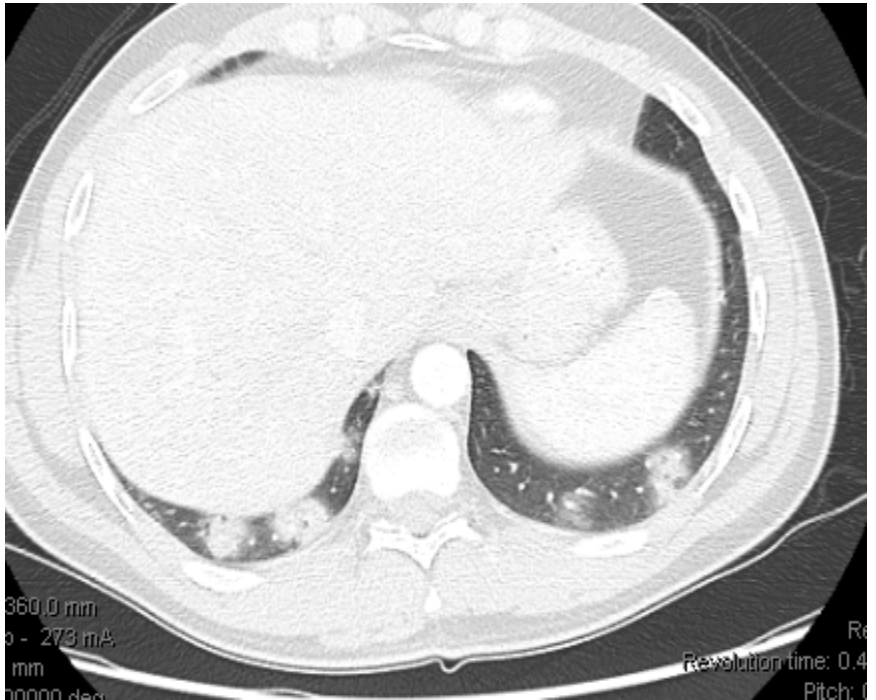
- 33-year-old man with melanoma, metastatic to the brain, liver and bone, presented with a **2-3 day history of generalized weakness, fatigue and progressive dyspnea**. Pembrolizumab was initiated 5 weeks prior after failing conventional therapies. The patient reported choking on his pills one day prior. He also complained of blurred vision, which he attributed to brain metastases. He denied cough, fevers or chest pain. No GI symptoms.
- Physical examination: is remarkable for generalized weakness, dyspnea on mild exertion and mild right ptosis with diplopia.

  Admitting studies:
  - Brain MRI: confirmed response to pre-existing brain metastases and no new lesions.
  - CBC: Hemoglobin 11.9 gm/dL; WBC 7.3 K/μL; Platelet count 231 k/μL differential wnl
  - CT chest: No PE; Pneumonitis versus pneumonia was suggested, Started on IV solumedrol (1 mg/kg/day) and empiric antibiotics.
- Two days later, respiratory symptoms progressed and the patient was placed on noninvasive ventilation (BIPAP). **Infliximab, dosed at 5 mg/kg** was started. **An arterial blood gas revealed: pH 7.25; pCO2 92 mmHg; pO2 138 mmHg; HCO3 41 on 30% FIO2**.
- The patient is transferred to the ICU and pulmonary consultation was requested









New nodular, ground glass and consolidative opacities predominantly in the lower lobes, most of which are ring shaped, suggesting reverse halo sign (atoll sign)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Question:

What is the most appropriate next step in evaluating this patient?

- 1. Bronchoscopy with biopsy of the lower lobe lesions
- 2. Increase steroid dose to 2 mg/kg/day
- 3. Start antifungal therapy
- 4. Serologic studies for antibodies to the acetylcholine receptor (AChR-Ab) and muscle-specific kinase (MuSK Ab)
- 5. Check T4 and TSH for ICI-related thyroid abnormalities

Answer:

What is the most appropriate next step in evaluating this patient?

- 1. Bronchoscopy with biopsy of the lower lobe lesions
  - No. May confirm organizing pneumonia, but will not explain diplopia, generalized weakness. Hypercapnic respiratory failure is disproportionate to degree of changes on CT.
- 2. Increase steroid dose to 2 mg/kg/day
  - No. Clinical response to steroids alone in the management of myasthenia gravis is slow (weeks). Also, steroids as first-line therapy may transiently worsen myasthenia gravis.
- 3. Start antifungal therapy
  - Atoll sign may be seen with fungal pneumonia, however the risk of fungal pneumonia in this patient is low
- 4. Serologic studies for antibodies to the acetylcholine receptor (AChR-Ab) and muscle-specific kinase (MuSK Ab)
  - Yes. Patient has classic signs and symptoms to suggest ICI-induced myasthenia gravis. Immediate work-up and treatment is warranted.
- 5. Check T4 and TSH for ICI-related thyroid abnormalities
  - Should be checked but will not explain all of the neurologic signs and symptoms.

Diagnosis:

- Additional work-up confirmed ICI-induced myasthenia gravis with myositis occurring concomitantly with ICI-induced organizing pneumonia (pneumonitis):
  - AChR-Ab was positive
  - MuSK Abs was negative
  - Creatine kinase - 3600 IU/L
- Treatment and outcome:

  Improved after IVIG and plasmapheresis, steroids and pyridostigmine.
  Discharged to rehabilitation facility

Other IrAEs associated with respiratory symptoms

- Hypercarbia: ICI-related myasthenia gravis, myositis
- Recent high dose steroid taper: Pneumocystis jirovecki pneumonia
- Generalized fatigue cold sensitivity weight gain: ICI-related thyroiditis
- Supraventricular tachycardia, lower extremity edema/volume overload, shock: ICI related myocarditis
- Increased tumor size/new lung lesions within first 1-2 cycles of ICI therapy: pseudoprogression
- Paratracheal/mediastinal/hilar lymphadenopathy: ICI-related sarcoid-like reactions

ICI-induced myasthenia gravis

- Rare (0.24%) of ICI-treated patients; but potentially deadly (up to 23% mortality
- Severe muscle weakness, rapid decline in respiratory function; may be associated with ptosis, diplopia and/or bulbar changes (dysphagia, dysphonia) as presenting signs/symptoms
- Myocarditis/myositis overlap in 1/3 of patients
- Arises typically after 1-4 cycles of ICI therapy
- IVIG with plasma exchange preceding or given simultaneously with steroids
- Rechallenge: safety is uncertain

Safa H et al. *J ImmunoTherapy of Cancer 2019*
Makarious D et al. Eur J Cancer 2017

Case Study #4

Immune Checkpoint Inhibitor Endocrinopathies- Diagnosis and Treatment

Mrs. Smith: History

55 y/o WF with malignant melanoma metastatic to bone and liver

- Treated with 4 cycles of immune checkpoint inhibitor therapy (ipilimumab and nivolumab) over 2.5 months

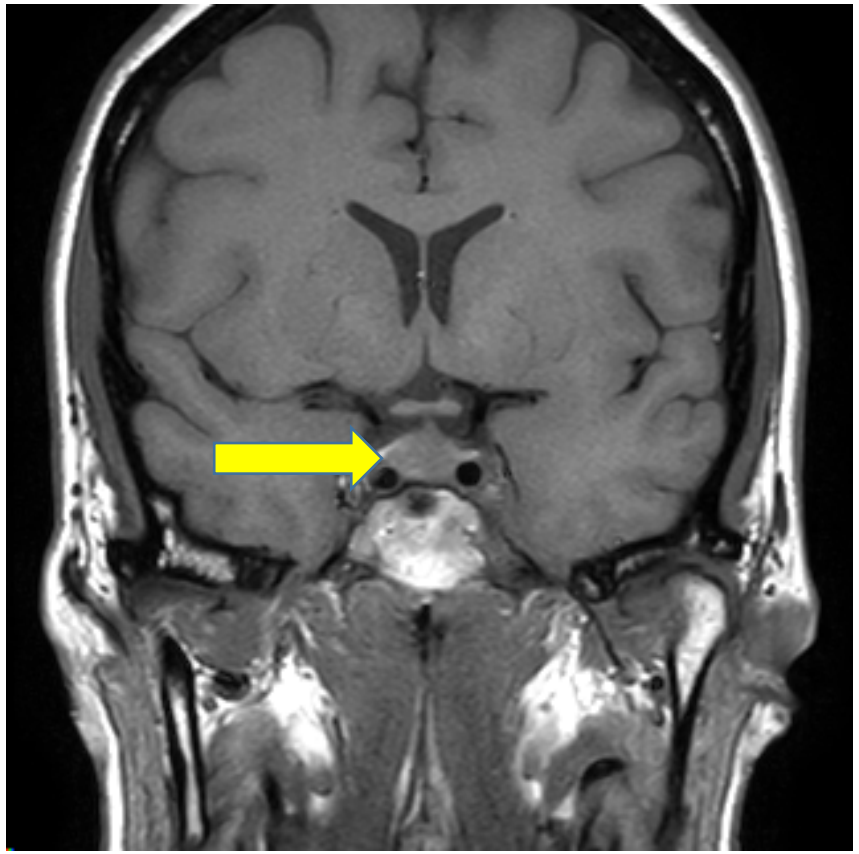
- Presented to ER with:
  - abdominal pain
  - diarrhea
  - polyuria
  - polydipsia
  - mild frontal headache

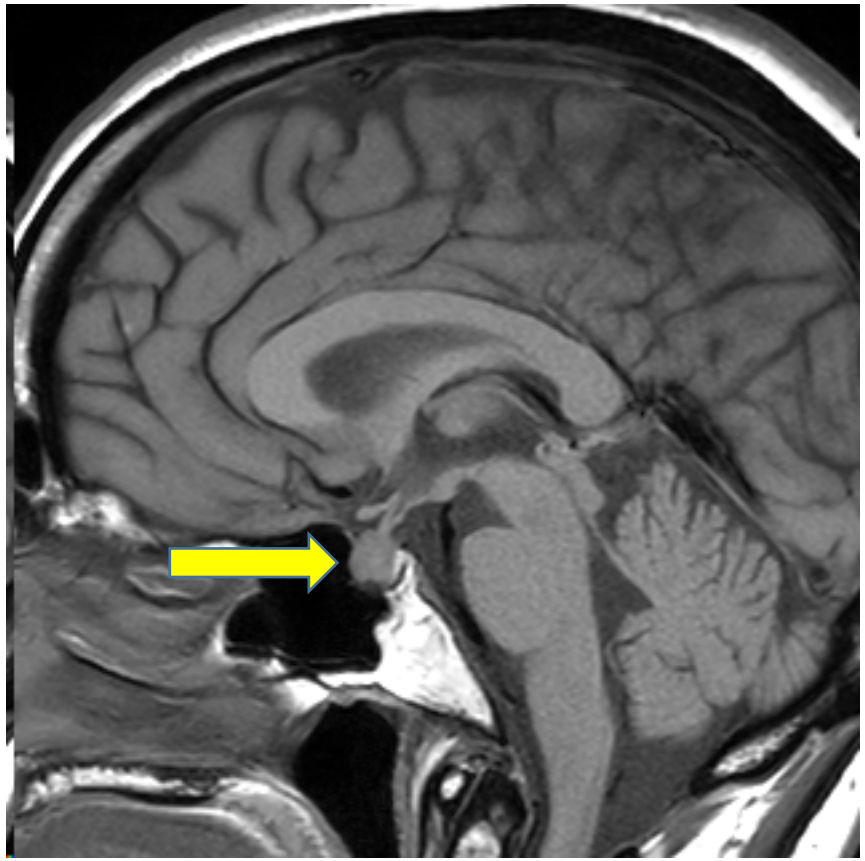
Mrs. Smith: Laboratory Data

ER Presentation

	2/7/2018 Pre-therapy	5/2/2018 2.5 mo of therapy
ACTH	21	7.5
CORTISOL, A.M.	15.5	**1.3 (L)**
GLUCOSE	77	**238 (H)**
Free T4	1.14	**0.64 (L)**
TSH	1.93	0.97

Mrs. Smith: Pituitary MRI





Which of the following is the likely cause for these symptoms and lab abnormalities?

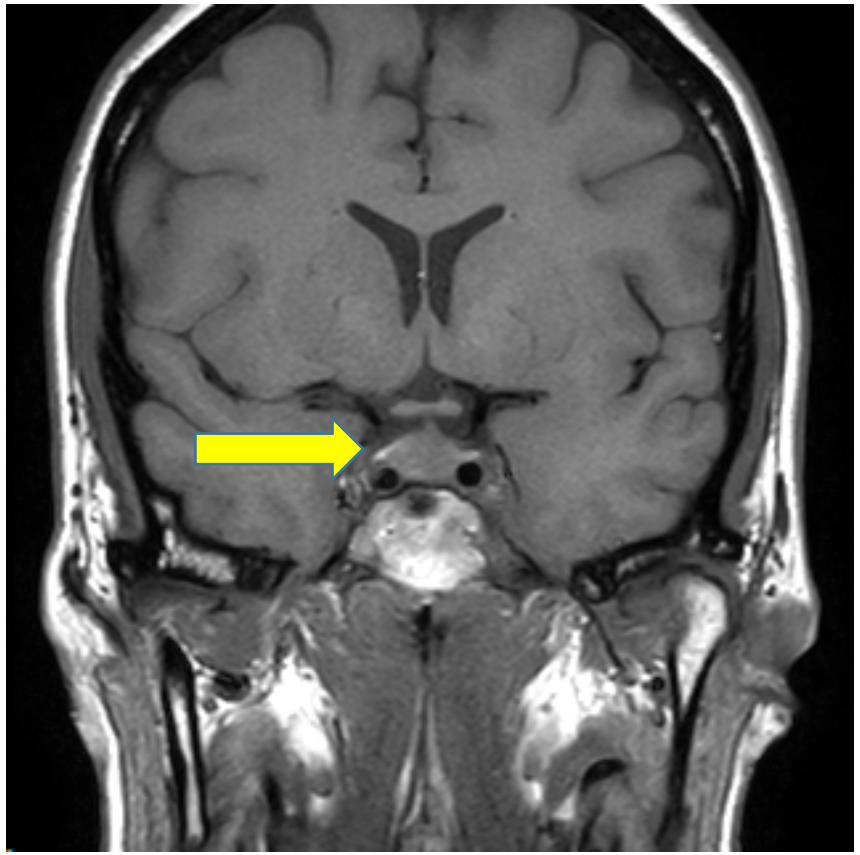
A. Brain Metastasis
B. Hypophysitis
C. Meningitis
D. Hemorrhage

Which medication(s) should Ms. Smith be started on?

A. Levothyroxine
B. Stress dose hydrocortisone followed by levothyroxine
C. Florinef
D. Levophed

Mrs. Smith

	2/7/2018 Pre-Therapy	5/2/2018 2.5 Mo Therapy	5/3/2018
ACTH	21	7.5	
CORTISOL, A.M.	15.5	**1.3 (L)**	
GLUCOSE	77	**238 (H)**	**329 (H)**
GAD-65 AB			**0.08 (H)**
C-PEPTIDE			**0.2 (L)**
Free T4	0.79 (L)	**0.64 (L)**	
TSH	0.81	0.97	



Which other endocrine problem does Ms. Smith have?

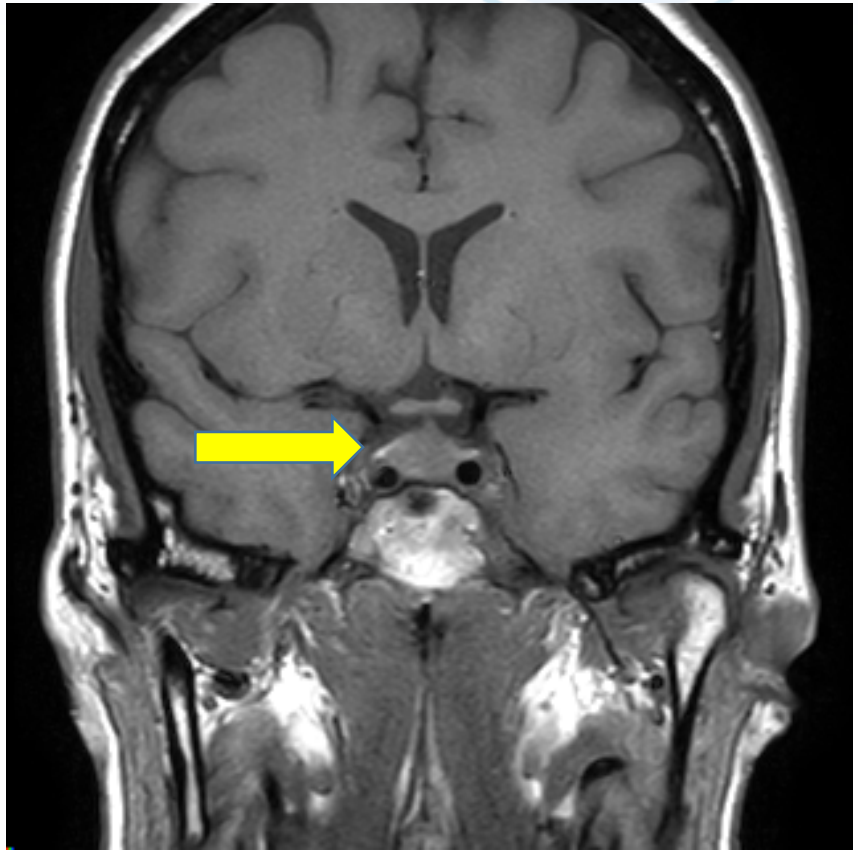
A. Stress Hyperglycemia
B. Infection
C. Autoimmune diabetes
D. Diabetic ketoacidosis

Question : Which Medication should Ms. Smith be started on for hyperglycemia?

A. Insulin
B. Metformin
C. Semaglutide
D. Glimepiride

Mrs. Smith: Diagnosis

	2/7/2018 Pre-Therapy	5/2/2018 2.5 Mo Therapy	5/3/2018
ACTH	21	7.5	
CORTISOL, A.M.	15.5	**1.3 (L)**	
GLUCOSE	77	**238 (H)**	**329 (H)**
GAD-65 AB			**0.08 (H)**
C-PEPTIDE			**0.2 (L)**
Free T4	0.79 (L)	**0.64 (L)**	
TSH	0.81	0.97	



Diagnosis:

- Hypophysitis with secondary hypothyroidism and adrenal insufficiency
- Diabetes

Rx: Treatment suspended and restarted in 7/2018 with Nivolumab

Case Study #5

- *Acute kidney injury in a patient with advanced renal cell carcinoma*

Reason for admission: Acute kidney injury

- 75 y/o male with metastatic right RCC presented for pre-op labs for cancer staging found to have a serum creatinine (Cr) of 6.94 mg/dl (baseline Cr 0.8-1.1 mg/dl). He states that he had Covid two weeks ago, but was relatively asymptomatic. He has no shortness of breath and is urinating well. Last dose of nivolumab 1/27/22.

- Renal cell ca history:
  - Diagnosed on 5/14/2021 with RCC and disease to retroperitoneal LN, lung, and bone (L4).
  - Initiated on 1st line therapy in June 11, 2021 with nivolumab (anti-PD1) and cabozantinib (9/2021, oral TKI).
  - Also underwent XRT for L4 lesion (6/18/2021).

PMH

- CAD s/p CABG x 2
- HTN
- Hypothyroidism

PSH

- Appendectomy
- Tonsillectomy

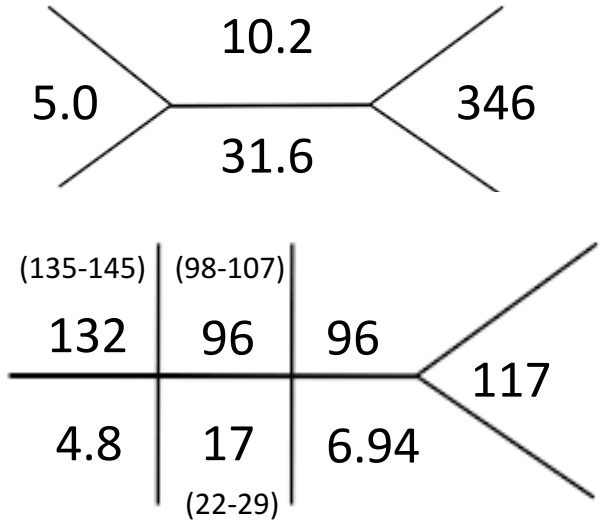
Allergies:

- Sulfa antibiotics

Medications

- Carvedilol 12.5 mg BID
- Losartan 100 mg Daily
- Aspirin 81 mg Daily
- Levothyroxine 50 mcg Daily

Labs



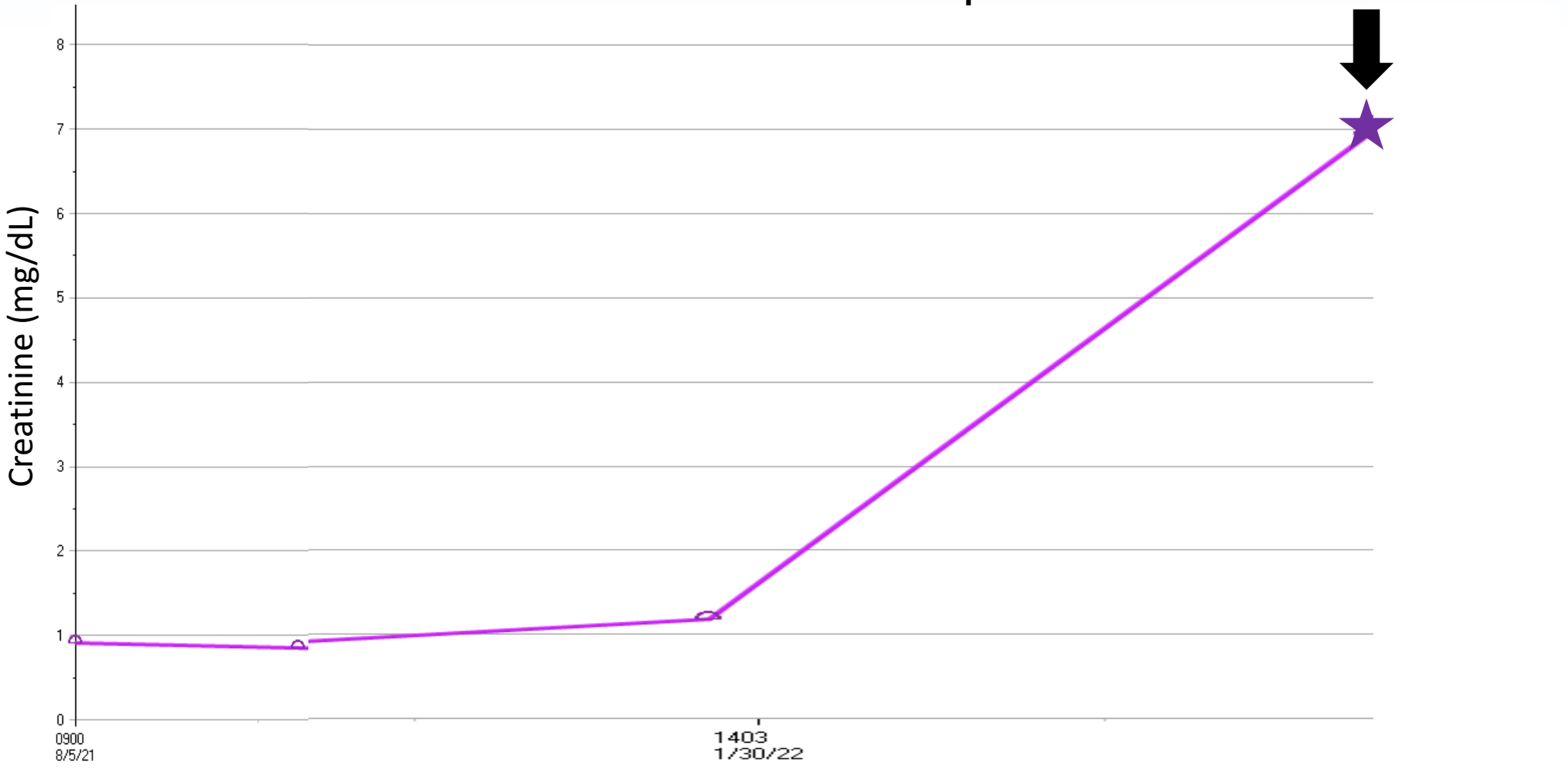
Physical Exam

- 129/64; 64; 20; afebrile,RA
- Gen: NAD, AxO/3
- HEENT: NC/AT, PERRLA, EOMI, MMM
- CV: RRR; no rubs/gallops
- Chest: CTA bilateral
- Abdomen: S/ND/NT
- Ext: trace LE bilateral edema

Renal US

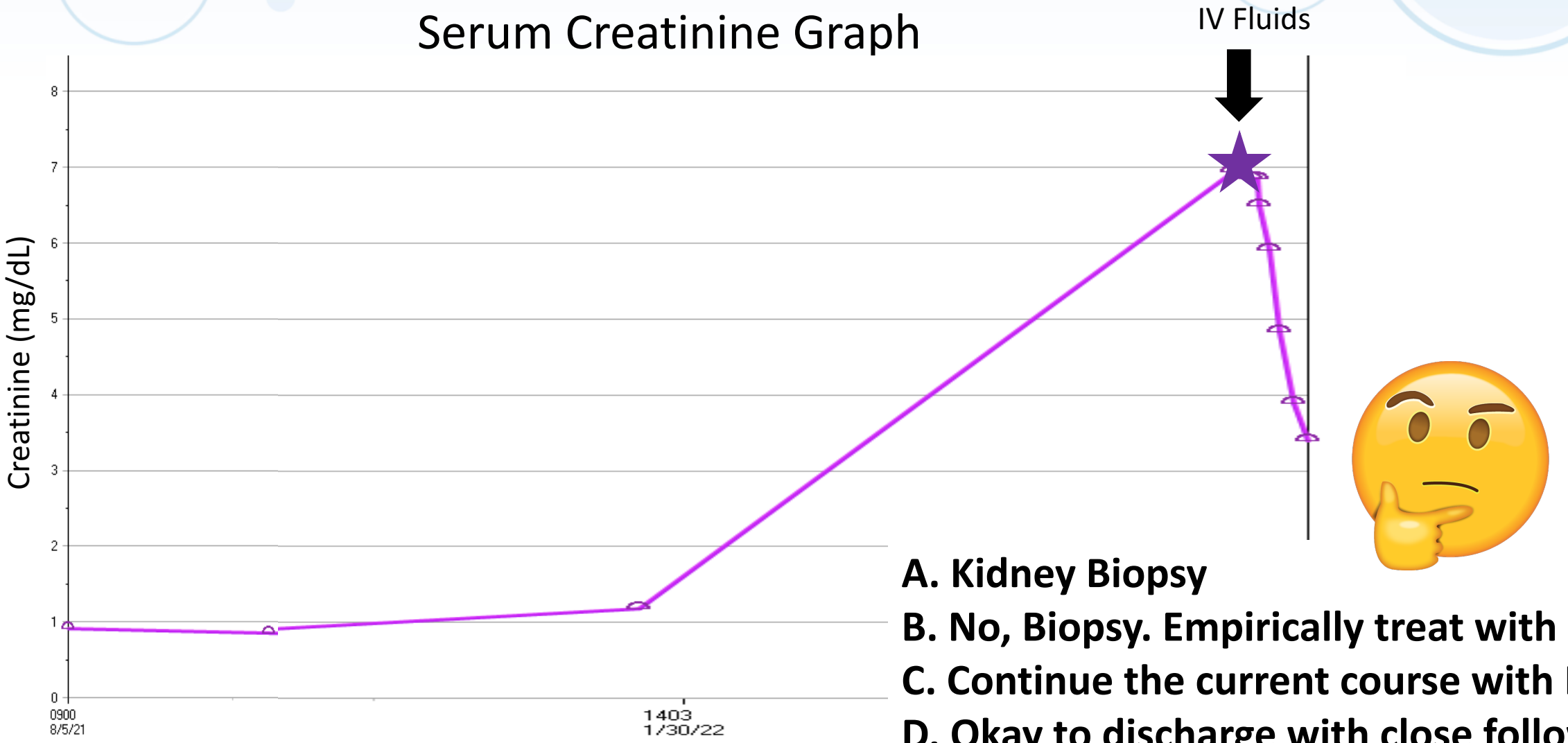
No evidence of hydronephrosis or nephrolithiasis. Mass of the lower pole of the right kidney.

Serum Creatinine Graph



	3/10/2022 2104
URINALYSIS	
UA Color	Straw
UA Appear	Clear
UA Glucose	NEG
UA Bili	NEG
UA Ketones	NEG
Specific Gravity U...	1.005
UA Blood	Moderate !
pH Urine	6.0
UA Protein	NEG
UA Urobilinogen	NEG
UA Nitrite	NEG
UA Leuk Est	Small !
UA WBC	16 * ▲
UA RBC	1 *
Squamous Epithelia...	NOT SEEN *
UA Bacteria	NOT SEEN *
UA Mucous	NOT SEEN *
CALCIUM/CREATININE	
U Calcium	2.1 *
OTHER RANDOM	
U Chloride	34 *
U Osmolality	203 *
U Potassium	14 *
U Sodium	43 *
CREATININE/PROTEIN	
U Creatinine	25.6 * ▼
U Prot/Creat	
UTP Rdm	

Serum Creatinine Graph



A. Kidney Biopsy
B. No, Biopsy. Empirically treat with steroids
C. Continue the current course with IV fluids
D. Okay to discharge with close follow-up

#LearnACI

Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,[1] Hamzah Abu-Sbeih,[2] Paolo Antonio Ascierto ,[3] Jill Brufsky,[4] Laura C Cappelli,[5] Frank B Cortazar,[6,7] David E Gerber,[8] Lamya Hamad,[9] Eric Hansen,[10] Douglas B Johnson,[11] Mario E Lacouture,[12] Gregory A Masters,[13] Jarushka Naidoo,[1,14] Michele Nanni,[10] Miguel-Angel Perales,[12] Igor Puzanov,[10] Bianca D Santomasso,[15] Satish P Shanbhag,[5,16] Rajeev Sharma,[10] Dimitra Skondra,[17] Jeffrey A Sosman,[18] Michelle Turner,[1] Marc S Ernstoff [19]

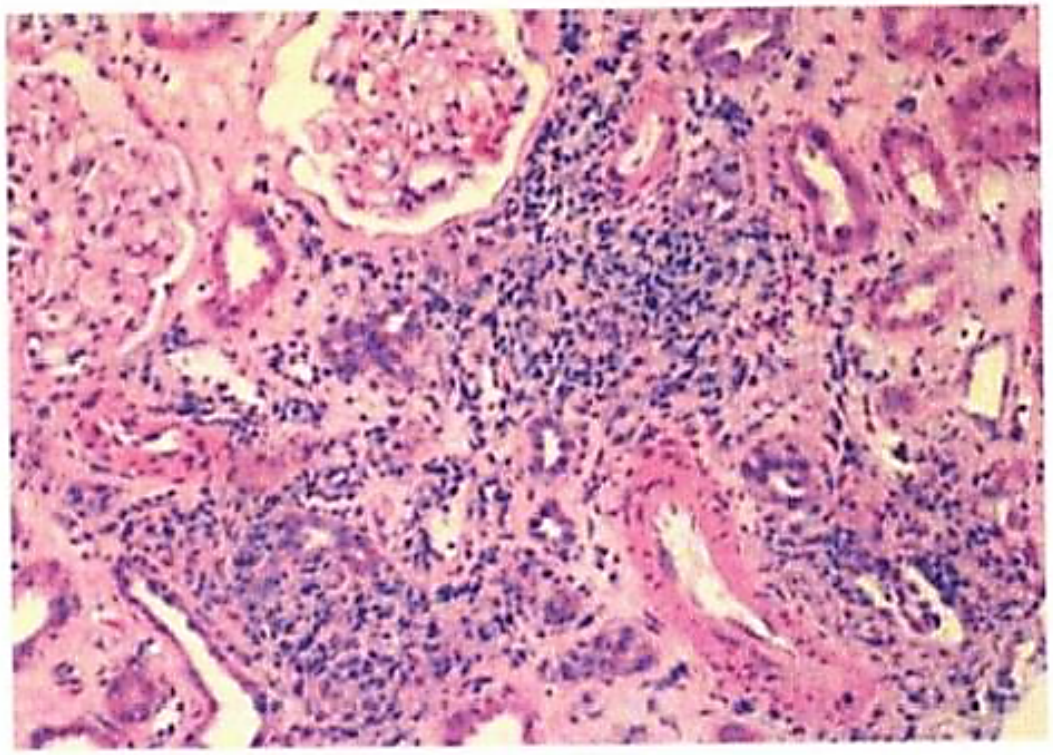
Renal toxicity panel recommendations

The following recommendations are intended to be used within the framework of toxicity management, including direction for at what grade of toxicity to hold and/or permanently cease treatment, considerations for life-threatening toxicities, as well as recommendations on optimal timing and dosing for administration of corticosteroids and/or other immunosuppressive agents by grade of AE, discussed in the **General panel recommendations** section. Any kidney-specific exceptions or additional considerations are noted in the recommendations below.

- Given the lack of specific clinical features for ICI-related AKI, renal biopsy should be strongly considered when feasible, particularly when a plausible alternative etiology for AKI exists or urine studies are suggestive of glomerular disease.

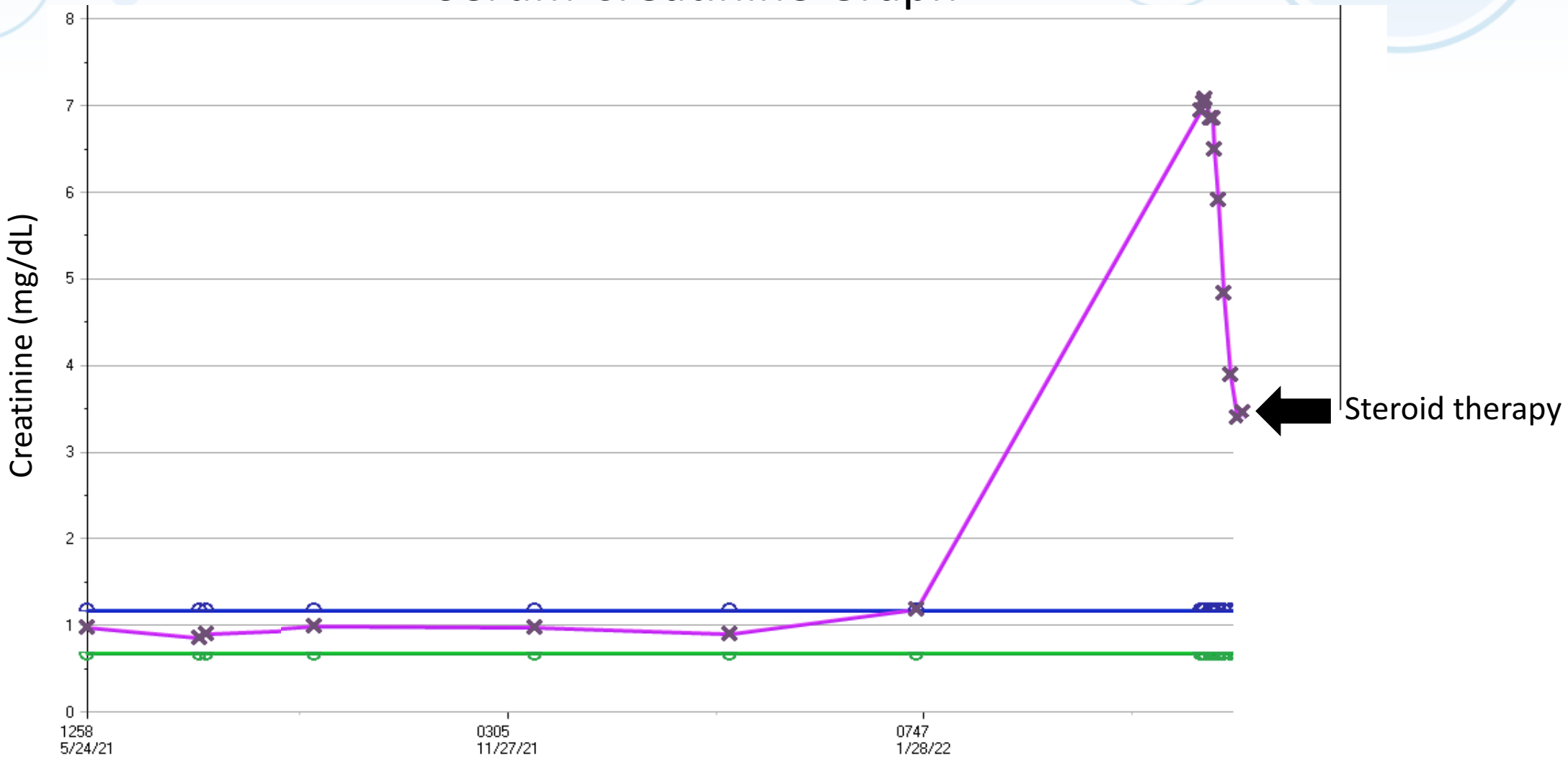
Correct answer: A: Kidney biopsy

Acute Interstitial Nephritis



H&E, interstitial nephritis

Serum Creatinine Graph



Rationale for kidney biopsy

- Recommend renal biopsy when feasible to help guide patient management from both a renal and oncological perspective
- Predominant renal lesion associated with ICI therapy is acute interstitial nephritis (AIN)
  - Treatment is corticosteroids
- Other kidney pathologies have also been reported where treatment requires immunosuppressive therapies

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