IMMUNE CHECKPOINT INHIBITORS NAVIGATING DIFFICULT TOXICITIES

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- No conflict of interest related to the content of this presentation
- No relevant disclosures to report
- **i3 Health and FLASCO have mitigated all relevant financial relationships**

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CASE PRESENTATION

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72 year-old male with PMH:

- HTN (poorly controlled on 2 antihypertensives)
- CKD – stage 3
- BPH

11/2017

- Evaluated by urology for gross hematuria for 6 weeks

- Cystoscopy negative

- CT scan demonstrated a 5 cm posteriorly located renal hilar mass. No evidence of disease elsewhere.

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01/2018

Left radical nephrectomy

PATHOLOGY

Subtype: **Papillary renal cell carcinoma (RCC)**

Size: 5.5 cm

TNM: pT1bN0M0

Stage: I

Nuclear Grade: 3 of 4

Sarcomatoid Differentiation: Present

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04/2019

- Patient then developed recurrence of papillary RCC in the periaortic and retroperitoneal lymph nodes
- Treated with cryoablation through interventional radiology

05/2022

- Surveillance imaging showed a 1 cm enhancing nodule at the superior aspect of the retroperitoneal ablation defect
- Underwent another ablation

Continued surveillance

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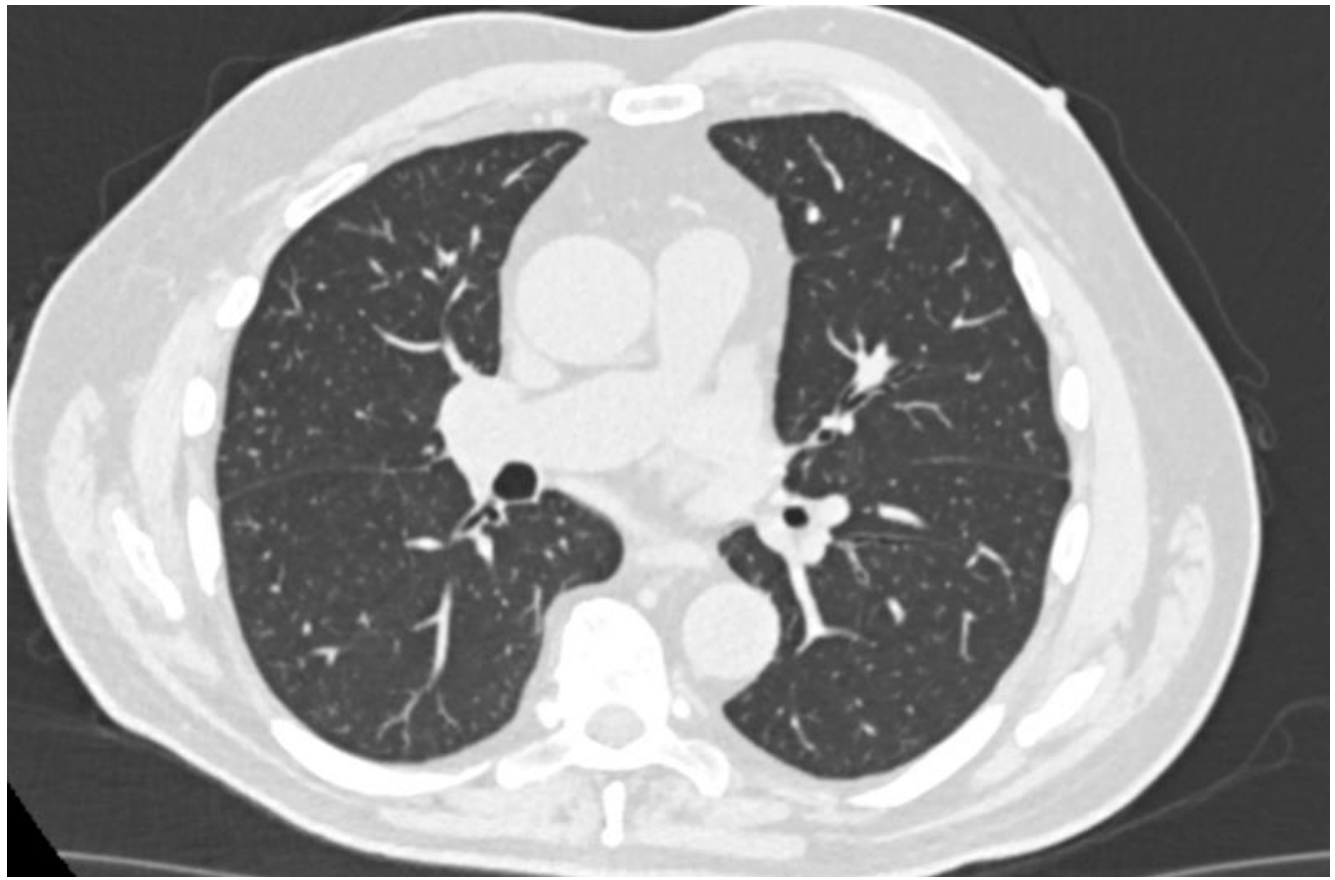
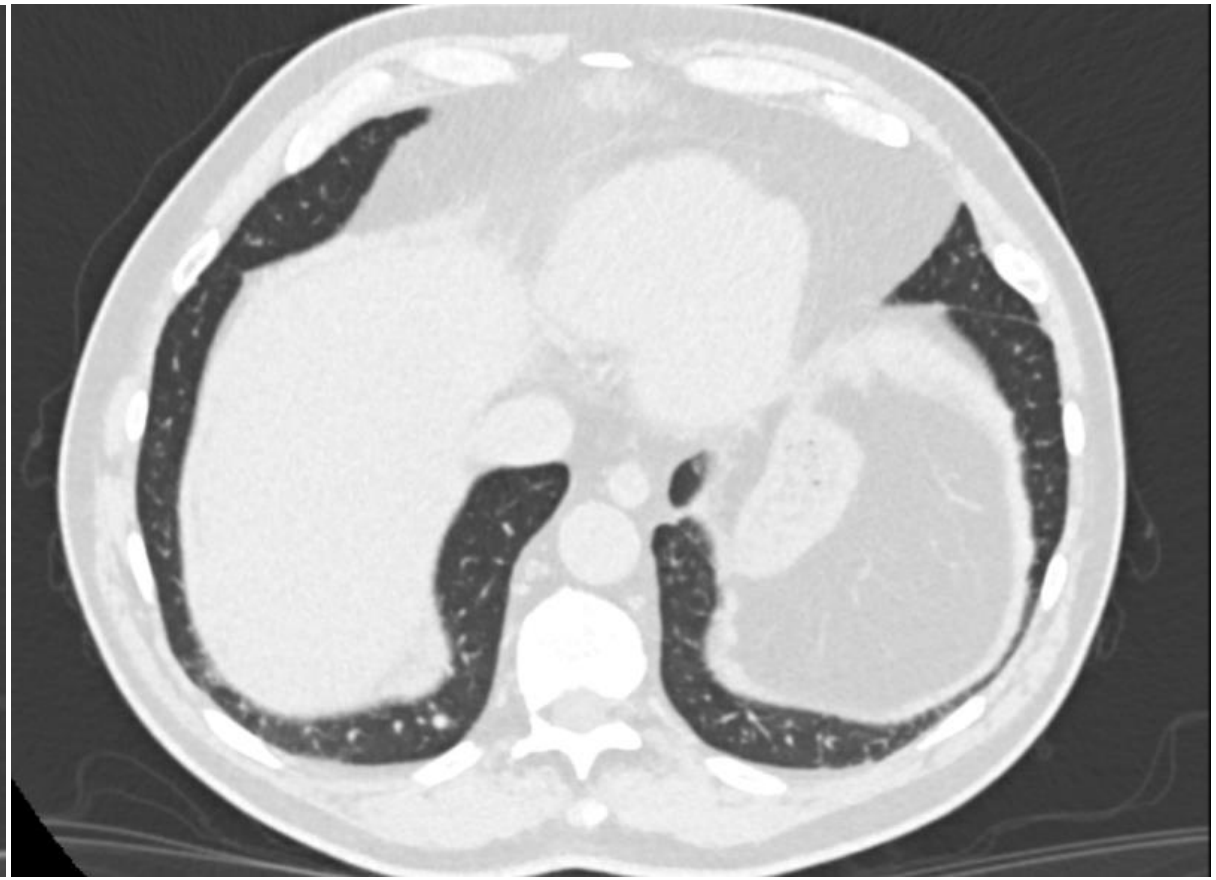
04/2024 - CT Chest





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08/2024

- Bronchoscopy/EBUS/Biopsy
- Pathology: **metastatic RCC with papillary features**

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09/2024

-Established care with us in the GU Medical Oncology clinic

-After discussing treatment options, mutual agreement on starting Ipilimumab/Nivolumab

-Started cycle 1

Ipilimumab 1 mg/kg

Nivolumab 3 mg/kg

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<u>3 weeks post cycle 1 Ipi/Nivo (pre-cycle 2 outpatient visit)</u>

- Maculopapular rash and arthralgias
- AST 560 (10x ULN) and ALT 268 (5x ULN)
  - US liver: negative
  - Viral hepatitis screen: negative
- Started prednisone 1 mg/kg with slow taper for ICI-related hepatitis and dermatitis
- Cycle 2 placed on hold

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Outpatient follow up 10 days later

- LFTs and rash improved with steroids
- Extreme fatigue and dyspnea on minimal exertion, progressive bilateral LE weakness, difficulties holding his head up
- Drooping eyelids and having a harder time keeping them open
- He feels worse towards the end of the day and better in the mornings
- Weakness started before starting prednisone

➢ **Directly admitted to the hospital**

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Notable physical exam findings on admission:

I. Hypophonia and muffled speech
II. Fluctuating dysarthria
III. Bilateral fatigable ptosis
IV. Diplopia
V. Power 4/5 (neck flexion/extension and bilateral arm abduction & hip extension)
VI. Hyporeflexia

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Inpatient workup

- Troponin (5th gen): 2350 (ref range <= 15 ng/L)
- EKG: RBBB, otherwise no abnormal findings
- Echo: mild LV strain and grade 1 diastolic dysfunction, otherwise no abnormal findings

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Inpatient workup

- Creatine Kinase: 1075 U/L (ref range <300 U/L)
- EMG: necrotizing myositis, however demyelinating disorders can not be ruled out
- Negative Inspiratory Force (NIF): -22 H20 cm
- MyoMarker3 profile: ordered

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DIAGNOSIS ???

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ICI-induced Overlap syndrome - Myopathy, Myasthenia Gravis, Myocarditis (The 3 M's)

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MANAGEMENT

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- Cardiology, Neurology, Rheumatology were all consulted
- The outpatient-prescribed prednisone was switched to IV high-dose methylprednisone (1g daily for 5 days) and then to continue PO prednisone 60 mg daily
- Plasma exchange (PLEX) – 5 sessions
  - Evidence indicates ICI myasthenia gravis confers higher morbidity compared to purely autoimmune myasthenia gravis
  - Evidence indicates that high dose steroids do not adequately treat myasthenia gravis and supports use of PLEX
  - MyoMarker3 profile came back negative (collected after PLEX)
- AchE inhibitor, Pyridostigmine 60 mg TID for symptomatic treatment
- Respiratory mechanics testing q4h

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- Clinically improving, but.. troponins are rising again!

10/30/24	04:59	1260 ▲
10/26/24	23:41	680 ▲
10/25/24	03:35	837 ▲
10/24/24	03:06	600 ▲
10/23/24	03:35	589 ▲
10/22/24	03:15	647 ▲
10/21/24	03:01	774 ▲
10/20/24	03:33	1265 ▲
10/19/24	05:29	2350 ▲

- EKG: new T-wave inversions in inferior leads
- Repeat Echo: no change in EF or LV strain

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Cardiology (concerned for steroid refractory ICI-induced myocarditis):

- Abatacept (IV loading dose 10 mg/kg) followed by SQ 10 mg/kg on days (day 5,14,28,42)
- Ruxolitinib 15 mg BID (abatacept has a delayed onset of response)
- Prednisone PO was increased to 1 mg/kg
- Mycophenolate avoided as telemetry monitoring showed episodes of NSVT (contraindicated with arrhythmias)

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Few days later: significant improvement and started the preparation for discharge.. BUT only then:

- Melena, BP 80s/40s
- Hemoglobin drop (10 → 7 g/dL)
- Lactate: 5.3
- POCUS: collapsable IVC
- EGD: oozing duodenal ulcer - clipped
- IR embolization (inferior pancreatic duodenal artery)
- PPI IV BID (was on prophylaxis pantoprazole PO 40 mg daily while on steroids)
- ICU care & PRBC transfusions

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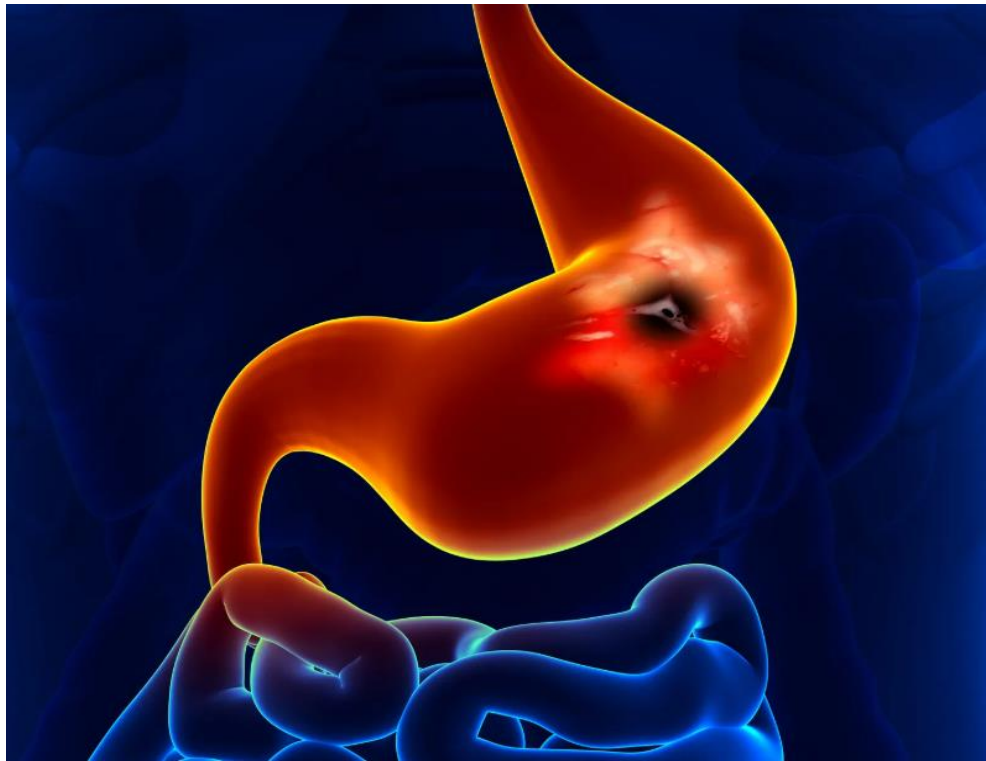
ICI → “itis” → high-dose steroids → GI ulcer and bleeding

STEROIDS.. Not always friendly!
-GI ulcers/bleeding
-Hyperglycemia
-Hypertension
-Osteoporosis/fractures
-Immune suppression/infections
-PCP pneumonia
-Adrenal suppression
-Anxiety/insomnia/psychosis



Just for some icing on the cake…

ICU/Hospital course further complicated by ***ESBL*** bacteremia

-Contact isolation

-Ertapenem 14 days

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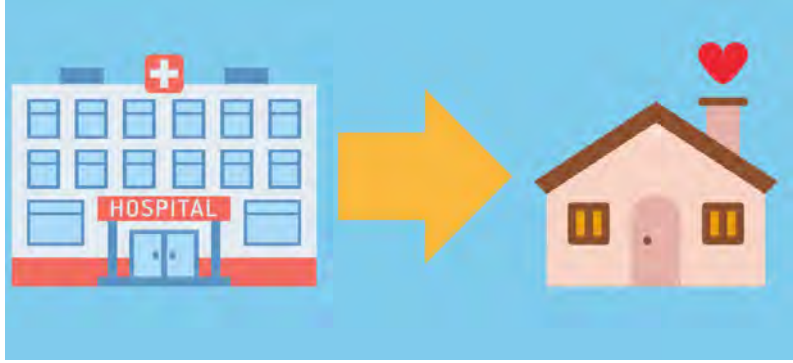

- Finally discharged home after a 21-day hospitalization!
- Slow taper of prednisone (1 mg/kg prednisone for 2 weeks, then a taper 5 mg weekly)
- Continued abatacept injections as scheduled
- Followed up in our oncology clinic – gradually regaining his function
- Plan from an oncology standpoint
  - Upcoming restaging scans in a few weeks
  - Continue observation if stable disease VS cabozantinib if notable disease progression

Immune Checkpoint Inhibitors: Promise vs. Risks

- Advantages:
  - Proven/Promising field with potential for durable responses
  - Less toxic than traditional chemotherapy
- Side Effects:
  - Autoimmune Syndromes (e.g., colitis, hepatitis, pneumonitis, 3 M's)
  - Endocrinopathies (e.g., thyroid disorders, adrenal insufficiency, diabetes)
- Challenges:
  - Serious, sometimes life-threatening side effects
  - Requires careful monitoring and management

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THANK YOU!