Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

# Case Study #1



#LearnACI

SK is a 70 yo female with metastatic melanoma from an unknown primary with bulky lymphadenopathy of the right axillary region.

- Being treated with neo-adjuvant Ipilimumab-Nivolumab
- Seen in clinic for clearance for dose #2
- Reported occasional loose stools improved with Loperamide

# When performing review of system, what should we ask SK to assess for immune-related gastrointestinal toxicities?

a. Number of stools per day
b. Change in stool consistency
c. Presence of blood or mucus in stools
d. Presence of abdominal cramps or pain
e. All of the above

- SK was cleared for dose #2 of Ipilimumab-Nivolumab with the addition of Budesonide
- Stools sent for lactoferrin and calprotectin
- 9 days later, patient notified team of bloody diarrhea multiple times per day
  - Upon further questioning patient stated she had bloody stool prior to dose #2

Which of the following should be part of SK's management at this time EXCEPT?

a. Send stools to work up infectious etiology
b. Initiate Prednisone 1 mg/kg/day
c. Initiate Methylprednisolone dose pack
d. Hold Ipilimumab-Nivolumab

- Patient was prescribed Prednisone 40mg BID (~ 1mg/kg/day) and instructed to continue Budesonide
- Stool studies revealed positive lactoferrin and elevated calprotectin (>1000)
- 2 days later, provider called patient to follow up and found that patient had not been taking the Budesonide correctly. Patient was instructed to continue both Budesonide and Prednisone

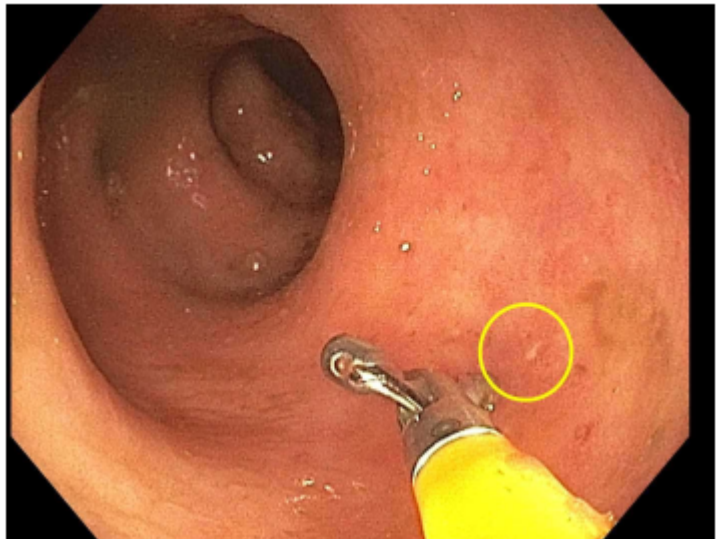
- 4 days later, patient reported that diarrhea has worsened to more than 8 stools/day
  - Instructed patient to go to local emergency department
- Patient was admitted to local hospital
  - Provider recommended the local provider increase Prednisone to 60 mg BID (~ 1.5mg/kg/day)
  - Patient was hospitalized for 3 days but there was no adjustment in Prednisone dose (remained on 40 mg PO BID)
  - Patient was discharged with instructions to discontinue Prednisone as “it was not helping” even though SK was having more than 10 bloody stools/day

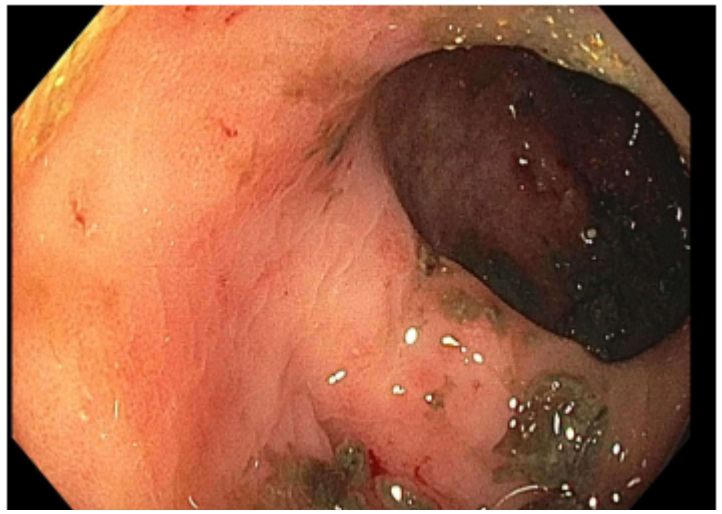
How would you communicate the treatment plan of immune-related colitis to local emergency provider to avoid what happened to SK?

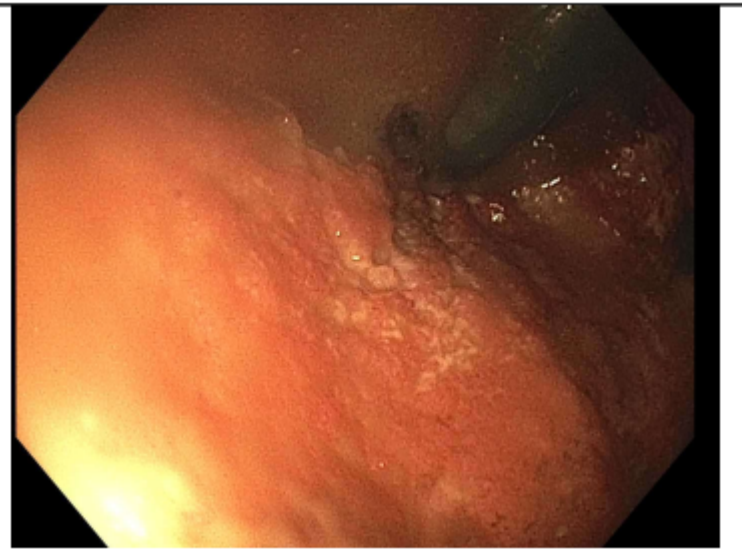
a. Explain the importance of corticosteroid dose adjustment
b. Describe the life-threatening potential of immune-related colitis
c. Advise to transfer patient to the Cancer Center once she was stabilized
d. All of the above

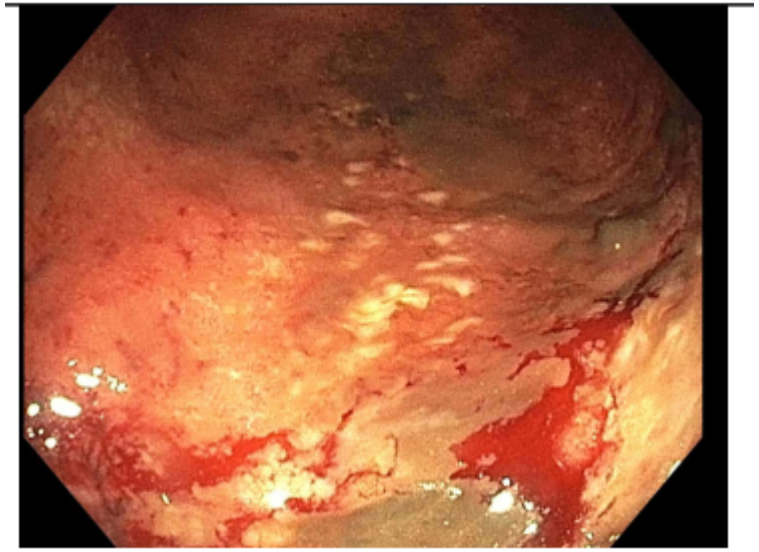
- Patient reported to the Cancer Center for further management
  - CT abdomen/pelvis showed thickened and edematous bowel walls
- Patient was hospitalized for 16 days
  - Initiated on Methylprednisolone 2 mg/kg/day
  - GI consult was obtained
  - Endoscopy showed pancolitis
  - Received 2 doses of Vedolizumab 2 weeks apart
  - Discharged on Prednisone 80 mg BID with taper plan
  - At time of discharge, diarrhea has resolved

# Colonoscopy

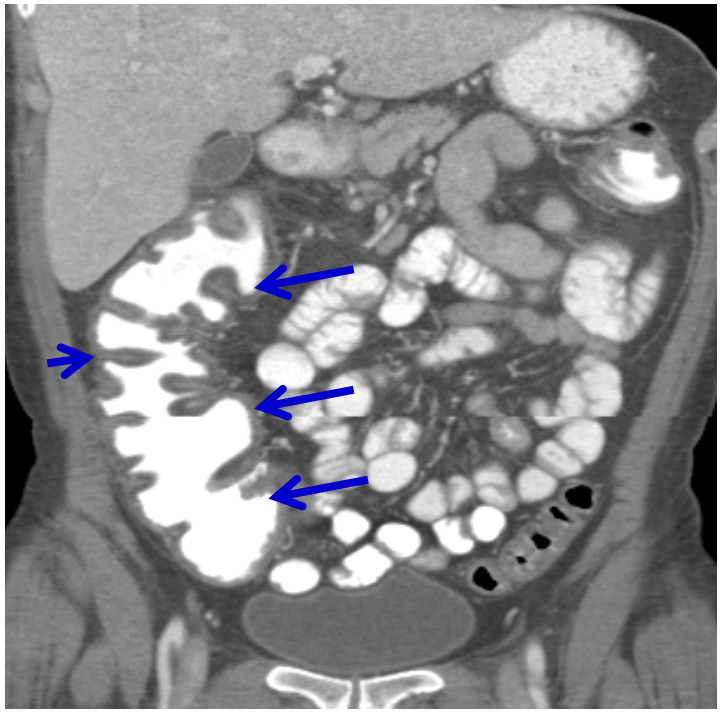


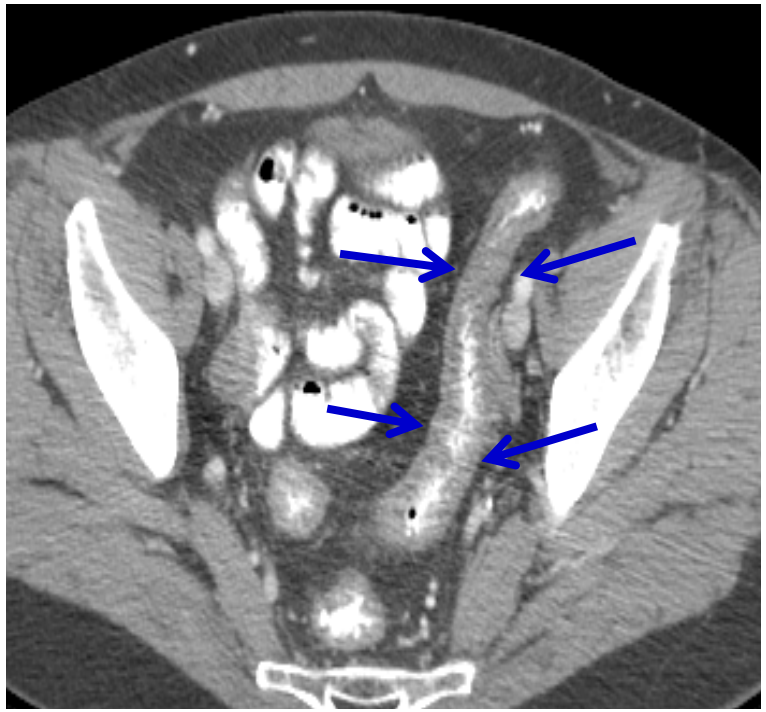






# CT Abdomen Pelvis





- 48 hours after discharge, patient called to report abdominal pain without diarrhea
  - Patient was prescribed Acetaminophen-Hydrocodone as needed for pain
- One day later, patient called to report recurrence of loose stool when at Prednisone 70 mg BID.
  - Patient was advised to increase Prednisone to 80 mg BID
- Two days later, patient presented to local emergency department for worsening pain, oliguria, and overall functional decline
  - CT revealed large volume intrabdominal free air
  - Patient underwent total colectomy due to perforations throughout the length of the colon

Questions for the panel:

1) What is the role of Budesonide in the management of immune-related colitis as the prevention trial with budesonide did not show any benefit?

Questions for the panel:

2) What is the role of fecal lactoferrin and calprotectin in the management of immune-mediated colitis?

Questions for the panel:

3) What would you do differently to avoid intestinal perforation in patients with immune-mediated colitis?

# Case Study #2

# Inmunotherapy related ocular adverse event in metastatic choroidal melanoma

- 60 years old female.
- Diagnosis: metastatic choroidal melanoma.
- 06-07-2019 treatment with Nivolumab and Ipilimumab was begun.
- 08-14-2019 a retinal ischemic lesion was documented.
- The patient maintained good vision (20/30), until radiation retinopathy was documented on 08/26/2020.

Calle-Vásquez A. MD.FACS.

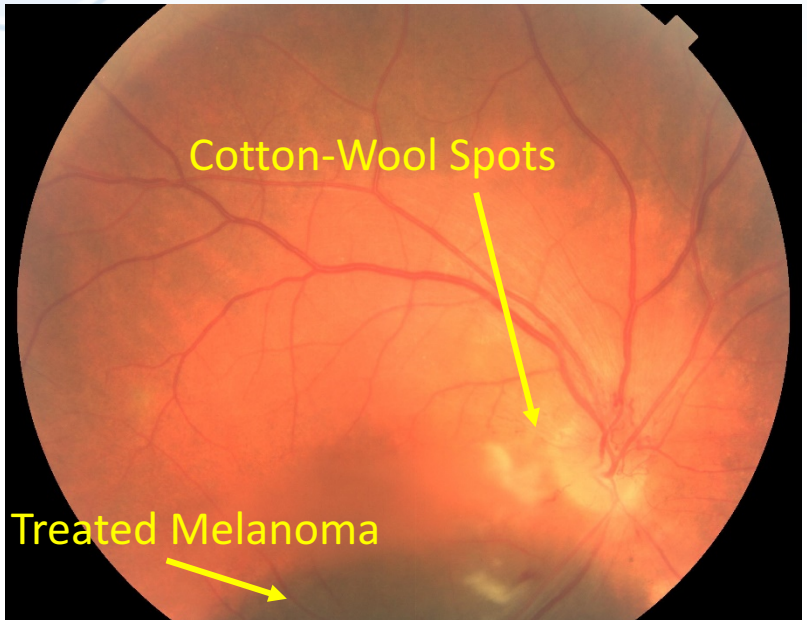
Lopez Mariana MD
(Fellow)

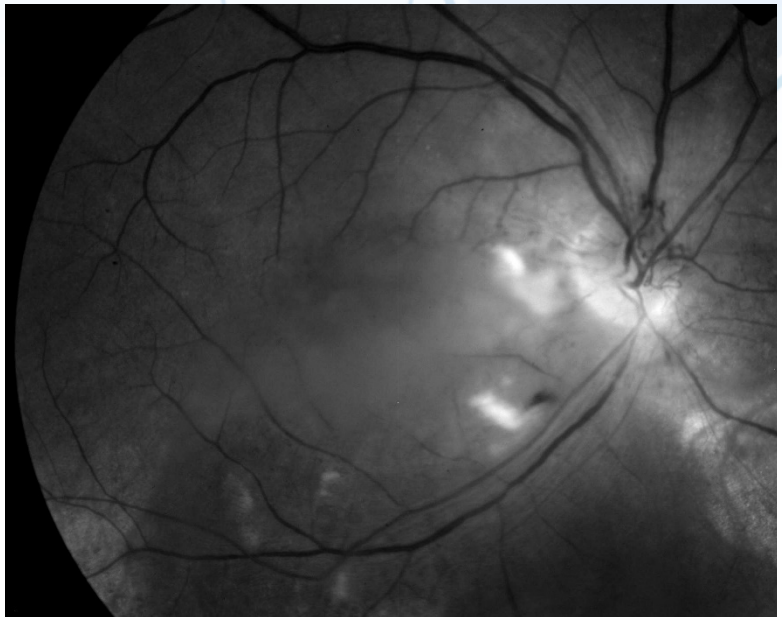
Calle Ophthalmic & Orbit Oncology Center

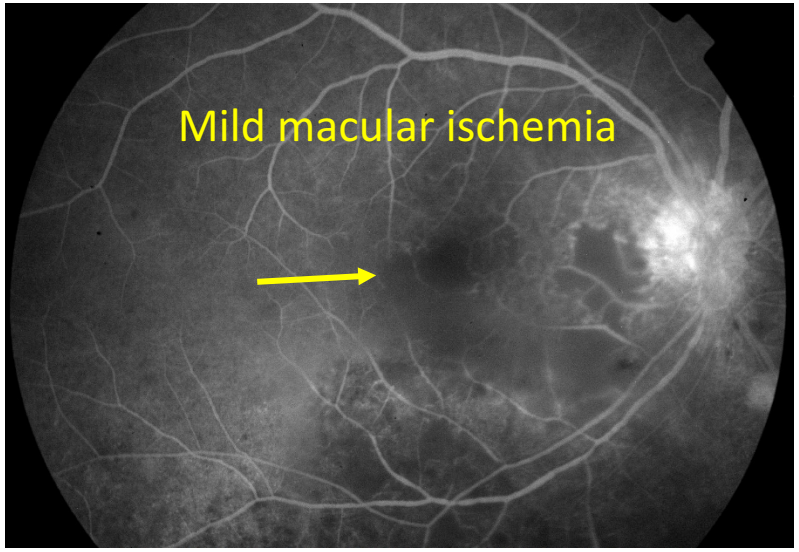
Bogotá.DC. Colombia.

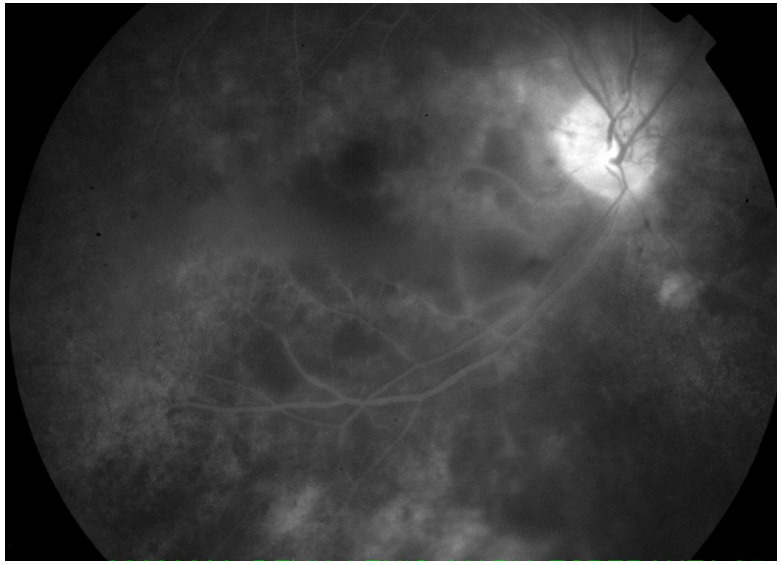
Intraocular

Anti-VGEF or Steroid advisable?





# Case Study #3

- 44 y.o. woman with PMH of renal transplants x2 (in 2000 and 2015, due to chronic rejection on tacrolimus 0.5 mg BID)
- Diagnosed with stage III colon cancer with high-risk features s/p right hemicolectomy followed by 6 months of adjuvant FOLFOX.
- Disease recurrence with carcinomatosis in 4 months. Treated with FOLFIRI with bevacizumab x 4 cycles
- Rapid disease progression. NGS done and showed KRAS: WT, pMMR, MSI stable, TMB at 49 (high).

Given the patient history, aggressiveness of disease, NGS of the tumor, would you consider immunotherapy?

A. Yes
B. No

Given the patient history, aggressiveness of disease, NGS of the tumor, would you consider immunotherapy?

A. Yes
B. No

If immunotherapy is considered, what is the risk of graft rejection?

A. 5%
B. 10%
C. 40%
D. 90%

If immunotherapy is considered, what is the risk of graft rejection?

A. 5%
B. 10%
C. 40%
D. 90%

If immunotherapy is given and rejection occur, what is your rescue regimen?

A. Methylprednisolone  IV 1-2 mg/kg/day
B. At least one drug other than corticosteroid
C. None of the above.

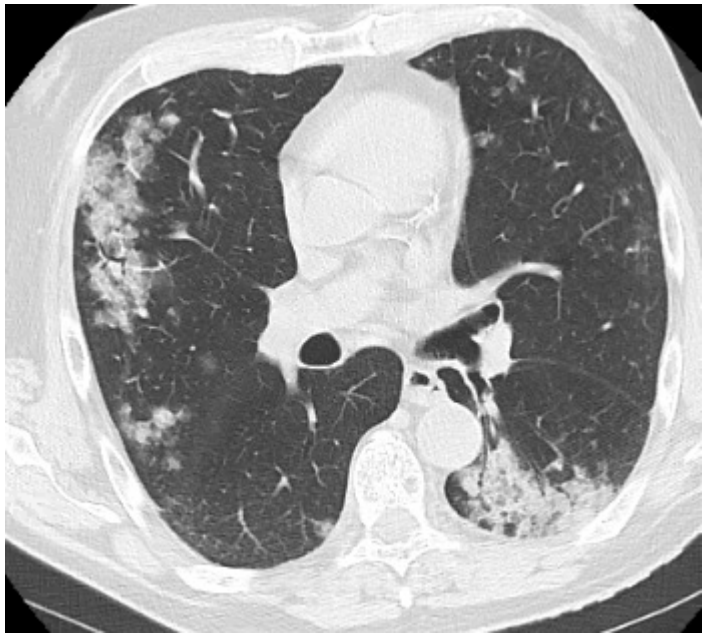
If immunotherapy is given and rejection occur, what is your rescue regimen?

A. Methylprednisolone IV 1-2 mg/kg/day
B. At least one drug other than corticosteroid
C. None of the above.

# Case Study #4

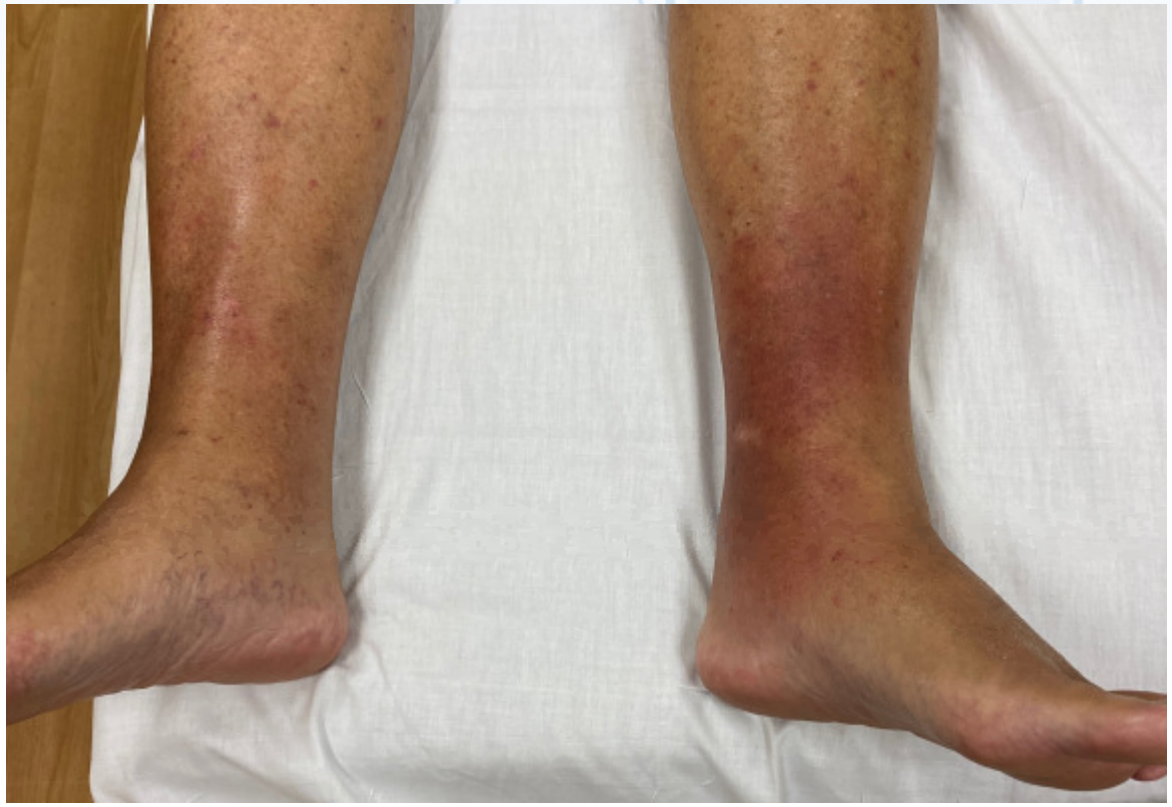
# Case Presentation

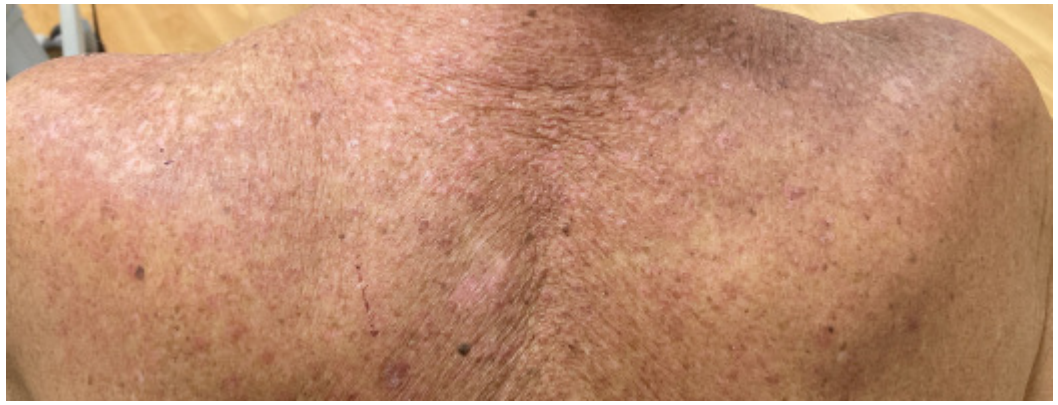
- Mid-70 year-old-male and never-smoker with previously local prostate cancer treated with radiation who presented with Stage IV (TX,NX,M1a) adenocarcinoma of the lung after ~5 months of increased cough and shortness of breath. Had multiple rounds of antibiotics given CT findings of multi-focal pneumonia prior to a bronchoscopy revealing mucinous adenocarcinoma.
- Moleculars: PDL1 - 5%, MSH6 L1330FS, ATM Splice site mutation, TMB 6, MSH6 expression intact on IHC, MSS



# Treatment History

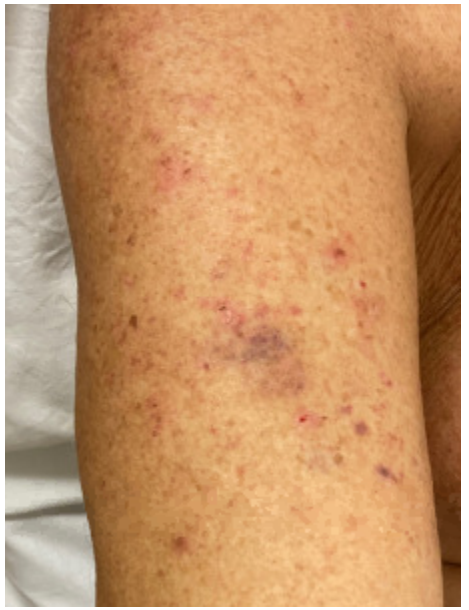
- C1 – carboplatin/pemetrexed/ pembrolizumab
  - Developed grade 2 LE edema bilaterally (DVT u/s negative) and grade 1 dermatitis on upper back. Prescribed betamethasone cream





# Treatment Continued

- C2- Held pembrolizumab due to G1 rash from previous cycle. Continued with Carboplatin/Pemetrexed.
- Developed G2 pruritic dermatitis on arms, torso back and lower legs. Re-developed lower-extremity edema.
- Prescribed prednisone taper

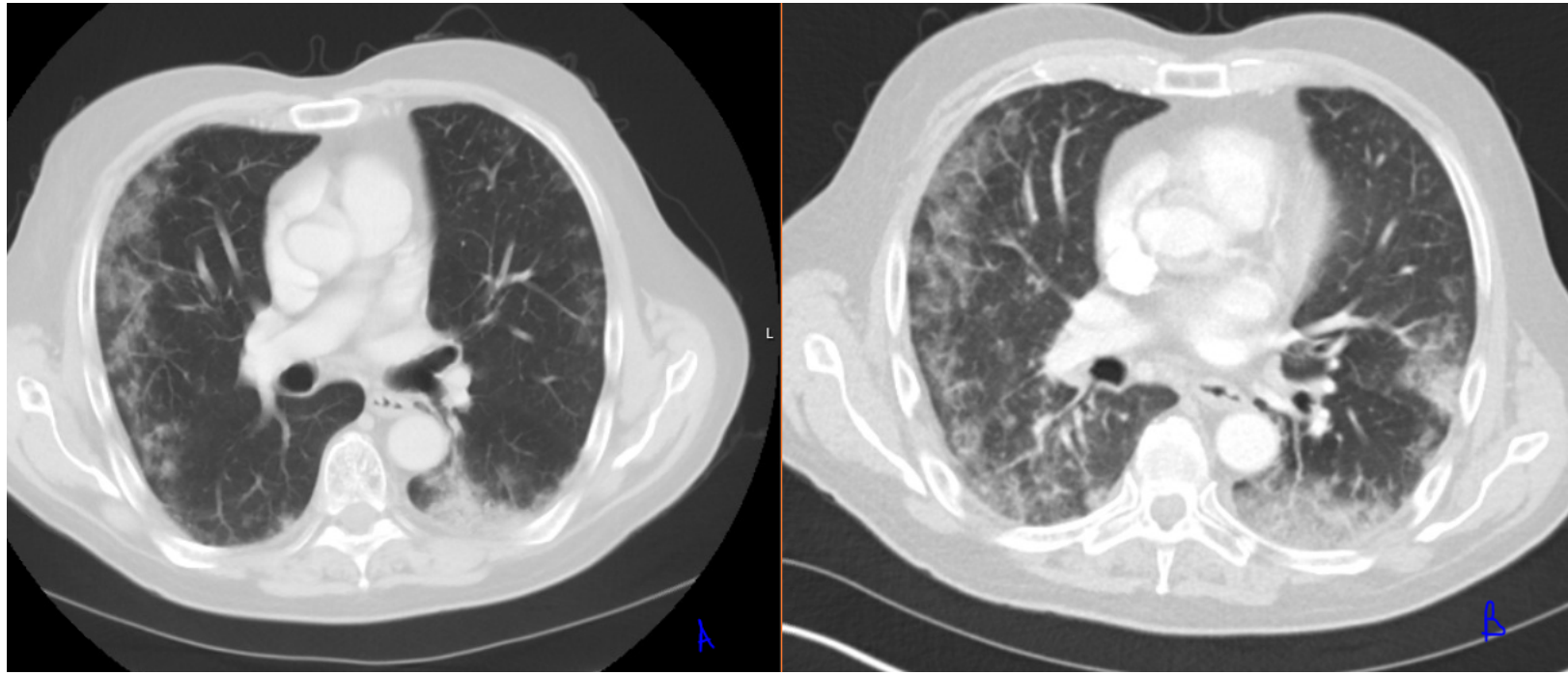


# Treatment Continued

- C3 – PR on restaging scans. Continued to hold pembrolizumab due to G2 rash from previous cycle. Continued with Carboplatin.
- C4 – Carbo/Pemetrexed at a dose reduction (Carbo AUC =4, Pemetrexed 400 mg/m2) given cytopenias with C3

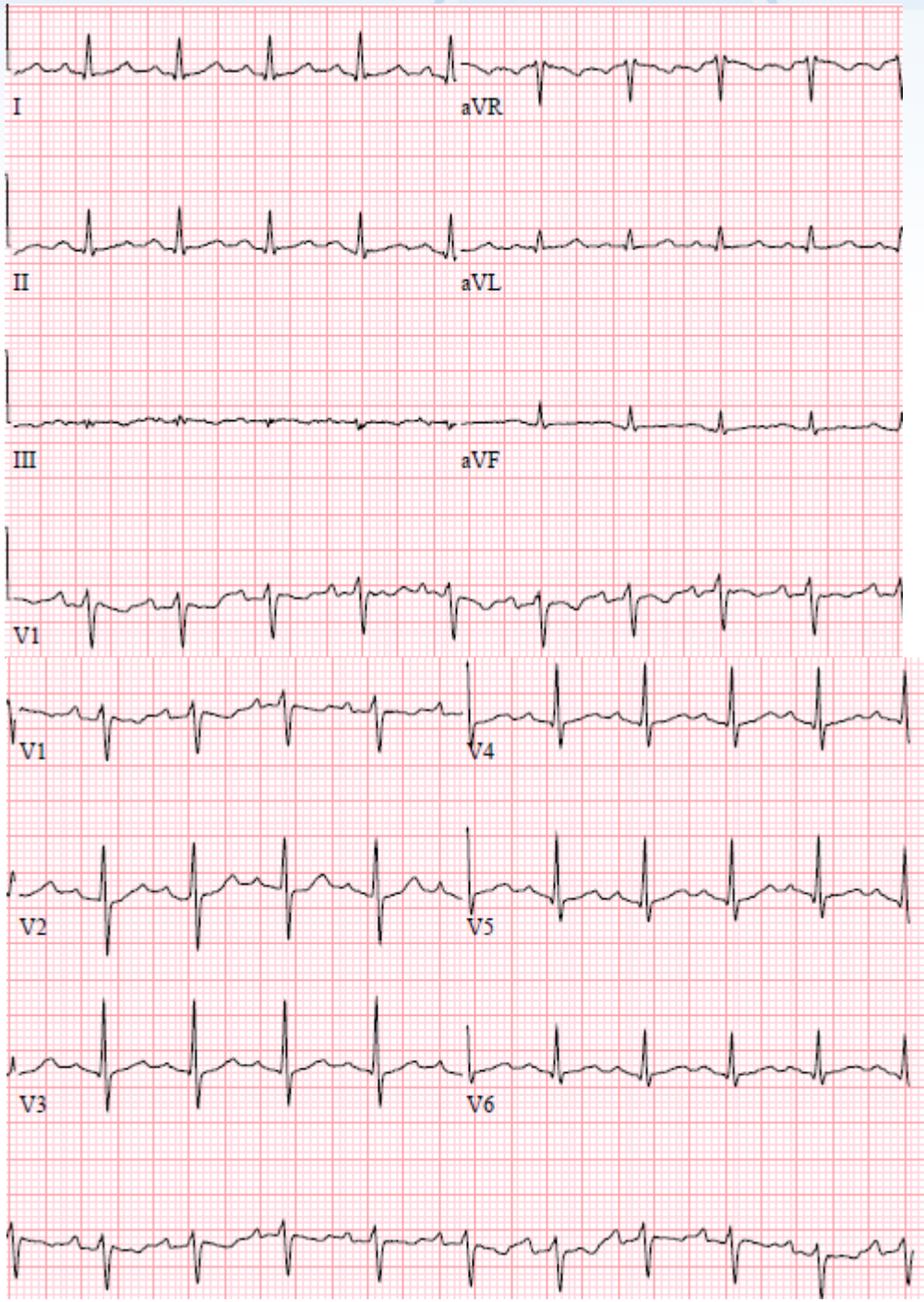
# Treatment Continued

- C5 – Had equivocal response on re-staging CT. Mutually decided to re-challenge with immunotherapy and add pembrolizumab to pemetrexed maintenance.
- Presented to clinic for C6 with worsening DOE (maintained adequate saturation with ambulation), neck weakness and tachycardia with exertion (HR 120-140s).



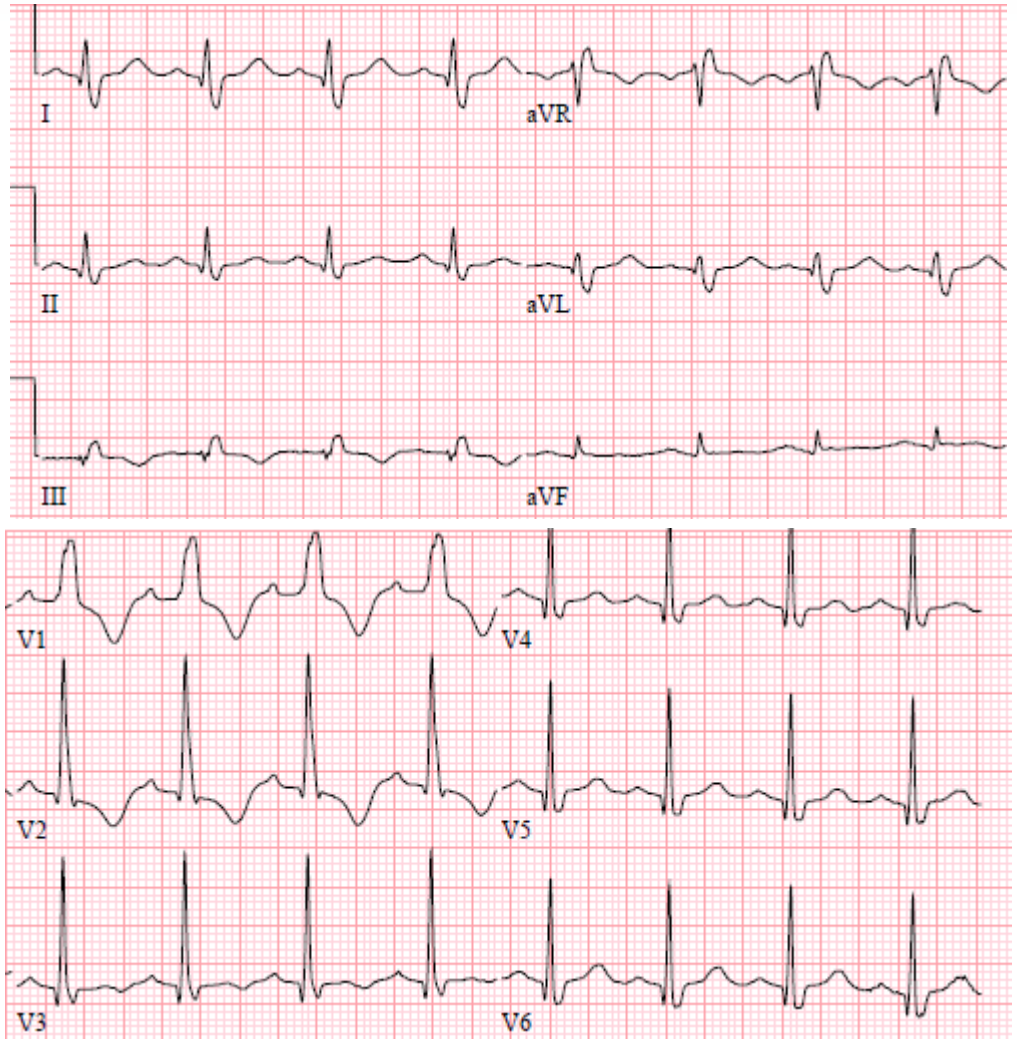
# Hospitalization

- Was admitted from clinic, developed fever to 101.4F on arrival to floor. Labs notable for CK of 5076, troponin of 2.59 ng/dl, AST/ALT 646/143.
- He was SARS-CoV-2 negative
- Echocardiogram unremarkable-preserved right and left ejection fraction with no wall motion abnormalities
- Was started on 2mg/kg/day of IV methylprednisolone. Fever resolved after starting steroids. Troponin down trended to 1.25. Given holidays, requested discharge. Was discharged on prednisone 80 mg daily with instructions to follow-up in clinic in one-week.



# Course Continued…

- One-week post-discharge follow-up- Troponin remained elevated at 1.01. New right-bundle branch block on ECG.
- Hospitalized and restarted on 2 mg/kg/day of IV methylprednisolone
- RBB resolved after increased steroid dose, LFT and Troponin down trended. Discharged on 110 mg of prednisone.



# Increased Weakness

- Seen in follow-up, endorsed ongoing weakness. Had neck extensor and proximal arm and leg weakness bilaterally. Also had a weak voice.
- Myomarker 3 profile negative (Anti-Jo-1 Ab, Anti-PL-7 Ab, Anti-PL-12 Ab, Anti-EJ Ab, Anti-Oj Ab, Anti-SRP Ab, Anti-Mi-2 Ab, Anti-TIF-1gamma Ab,Anti-MDA-5 Ab, Anti-NXP-2 Ab, Anti-PM/Scl-100 Ab, Anti-Ku Ab, Anti-SS-A Ab, Anti-U1 RNP Ab, Anti-U2 RNP Ab, and Anti-U3 RNP Ab)
- VGCC Antibody negative
- Myasthenia Gravis Panel 3
  - Acetylcholine Receptor Binding Antibody elevated 0.85 nmol/L ( Negative: < or =0.30 nmol/L , Equivocal: 0.31-0.49 nmol/L , Positive: > or =0.50 nmol/L)
  - Acetylcholine Receptor Blocking Antibody negative
  - Acetylcholine Receptor Modulating Antibody negative
  - Striated Muscle Antibody Screen positive (1:80)

# EMG

**IMPRESSION:**
1. **Nerve conduction studies are consistent with a distal symmetrical axonal sensorimotor polyneuropathy.**
2. **Electromyography shows evidence of a chronic neuropathic process. Findings also consistent with a chronic myopathy.**

- Felt findings from EMG (~3 mo after initial hospitalization) were related to “recovery myopathy.”
- Continues with physical therapy after long-prednisone taper. Had PR on re-staging scans after immune-related toxicity. Remains off cancer-directed therapy at this time.

# Discussion points

- Median number = 1 dose of ICI
- Only 18% had low EF, 67% had an arrythmia.
- (Immune Checkpoint Inhibitor-Induced Myocarditis with Myositis/Myasthenia Gravis Overlap Syndrome: A Systematic Review of Cases - PubMed (nih.gov)).

- 65 pt case series, 38% fatality rate attributed to MG complications. Upfront IVIG or PLEX associated with better outcome than steroids alone (improvement in symptoms 95% v 63%).
- Outcomes in ICI-induced MG- Immune checkpoint inhibitor related myasthenia gravis: single center experience and systematic review of the literature | Journal for ImmunoTherapy of Cancer | Full Text (biomedcentral.com)

# Discussion Continued

- What percentage of patients with low-grade iRAE, when re-challenged, develop higher-grade toxicity?
- 24 079 irAE cases associated with at least 1 ICI were identified using pharmacovigilance database
- 28.8% recurrence rate of the same irAE after rechallenge with the same ICI, different irAE occurred in 4.4% of patients (Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events in Patients With Cancer | Targeted and Immune Cancer Therapy | JAMA Oncology | JAMA Network)
- 118 with irAE from single-institution, The rechallenge of ICI after mild or severe irAE was associated with 60% of irAE grade ≥2 recurrence or new irAE. (Safety assessment of anti-PD(L)1 rechallenge after immune-related adverse events - Annals of Oncology)

# Case Study # 5

ME is a 31-year-old female with V600E-positive stage IV melanoma with lung and brain metastases (diagnosed 8/2019).

- PMH: Crohn's disease
  - ❖ Diagnosed 2003, s/p partial small bowel resection for small bowel obstruction.
  - ❖ Past therapies for Crohn's disease: mesalamine, corticosteroid, mercaptopurine for short period of time; never used any biologics
  - ❖ Off all treatments for the past 9 years

- ME was treated with craniotomy with excision of the right parietal mass followed by stereotactic radiosurgery to 3 smaller brain lesions then targeted therapy (Encorafenib-Binimetinib).
- Restaging at 3-month showed a partial response in the lung lesion and a new brain metastasis (treated lesions were stable). The oncologist considered adding checkpoint inhibitor to targeted therapy.

1) What should we consider before adding anti-PD1 to treat ME?

a. Consult GI specialist to establish care

b. Consider chemotherapy option for melanoma treatment

c. Discuss risk and benefit of anti-PD1 with patient

d. A and C

e. B and C

- GI consult: Colonoscopy showed no evidence of inflammation. Fecal lactoferrin: negative. Fecal calprotectin: 98.8 (normal: ≤ 50 mcg/gm)
- GI specialist recommended to proceed with nivolumab and planned to use vedolizumab concurrently with nivolumab if patient had flare up symptoms of Crohn's disease
- Labs for clearance of dose 2 nivolumab (in combination with targeted therapy): ALT 1193, AST 902, Alkaline Phosphatase: 209, Total Bilirubin 9.2

2) What is the risk for the development of de novo irAEs in patients with pre-existing autoimmune disease in general?

a. 10-20%

b. 30-40%

c. 50-60%

d. > 70%

- ME was admitted for immune-mediated hepatitis
  - ❖Consulted hepatology
  - ❖ Negative serology for viral hepatitis, ANA, ASMA, LKM-1, AMA
  - ❖ Ceruloplasmin within normal limit
  - ❖ Liver biopsy: marked acute hepatitis with centrilobar necrosis and pericellular fibrosis.

- ME also had loose and watery diarrhea on admission.
  - ❖ Fecal lactoferrin: positive
  - ❖ Fecal calprotectin: 678 (baseline 98.8 mcg/gm; normal: ≤ 50 mcg/gm)
  - ❖ Negative infectious disease work up
  - ❖ Colonoscopy: mild active ileitis; reactive colonic mucosa with mild architectural distortion and increased crypt apoptosis
  - ❖ High concern for Crohn's disease flare vs immune-related enterocolitis
  - ❖ GI specialist planned to treat with vedolizumab once patient is tapered off mycophenolate.

- ME's immune-mediated hepatitis and colitis management
  - ❖ Held Nivolumab and Encorafenib-Binimetinib
  - ❖ Started on Methylprednisolone 2mg/kg/day IV and mycophenolate 1 gram PO BID
- Patient was discharged with Prednisone taper over 4 weeks (hospitalized for 18 days).

- 1 month after discharge, restaging showed progressive disease in the lungs and brain. LFTs down to grade 1. Continued Prednisone and Mycophenolate taper. Resumed targeted therapy.
- 3 months after discharge, restaging showed further progression in lungs, new liver metastases and stable disease in the brain. Had completed Prednisone and Mycophenolate taper.

- After risk/benefit discussion, ME was rechallenged with concurrent Nivolumab + Tocilizumab 8 mg/kg. Received 4 cycles of Nivolumab. Tocilizumab discontinued because of severe infusion reaction at dose 3. No flare up of Crohn's disease symptoms. LFTs remained within normal limit.
- Restaging after cycle 4 Nivolumab: marked progression with increasing sizes and numbers of numerous lung and liver metastases, new abdominal lymphadenopathy, bilateral adrenal, muscular, and subcutaneous metastases.

- Changed treatment to Ipilimumab- Nivolumab. Had many flare up episodes requiring treatment interruptions. GI specialist treated with infliximab x 3 then vedolizumab x 3 then ustekinumab.
- 18 months later (4/20/22), restaging: stable treated brain metastases, stable extracranial disease with no focal FDG activity per PET-CT. Received cycle 19 nivolumab maintenance with concurrent ustekinumab 90 mg SC every 8 weeks. Continued to have grade 1 diarrhea. Fecal calprotectin 201 mcg/gm.

# Question for the panel

What is the impact of selective immunosuppressive agents (such as tocilizumab, infliximab, vedolizumab, ustekinumab, etc…) on anti-tumor activity of checkpoint inhibitors if used concurrently?

# Case Study # 6

- 64 y.o. male with history of Hepatitis C infection treated with interferon in the past and cirrhosis (Child A, MELD Na 19 initially) presented with abd pain and found to have liver mass.
- MRCP showed cirrhosis with 6.8 cm right hepatic lobe mass in Seg 7 compatible with HCC LIRADS 5 with extension of the mass into the porta hepatis. AFP 43. CT chest showed no metastasis to the lungs.
- Treated with SBRT for 5 fractions then started on Atezolizumab plus bevacizumab. After 6 cycles of IO combination, significant treatment response with decrease in size of seg 7 mass to 3 cm. Previously seen periductal extension towards the liver hilum is not seen any more (CR).

1) Can you consider this patient for liver transplant given he is now within Melan criteria however in the setting of immunotherapy use? What is the OS for each modality offered below?

A. No. Continue Atezolizumab plus bevacizumab

B. Yes. Evaluate for orthotopic liver transplantation