Immunotherapy and Side Effect Management: Challenging Cases

Miami Cancer Meeting
March 29-31, 2019

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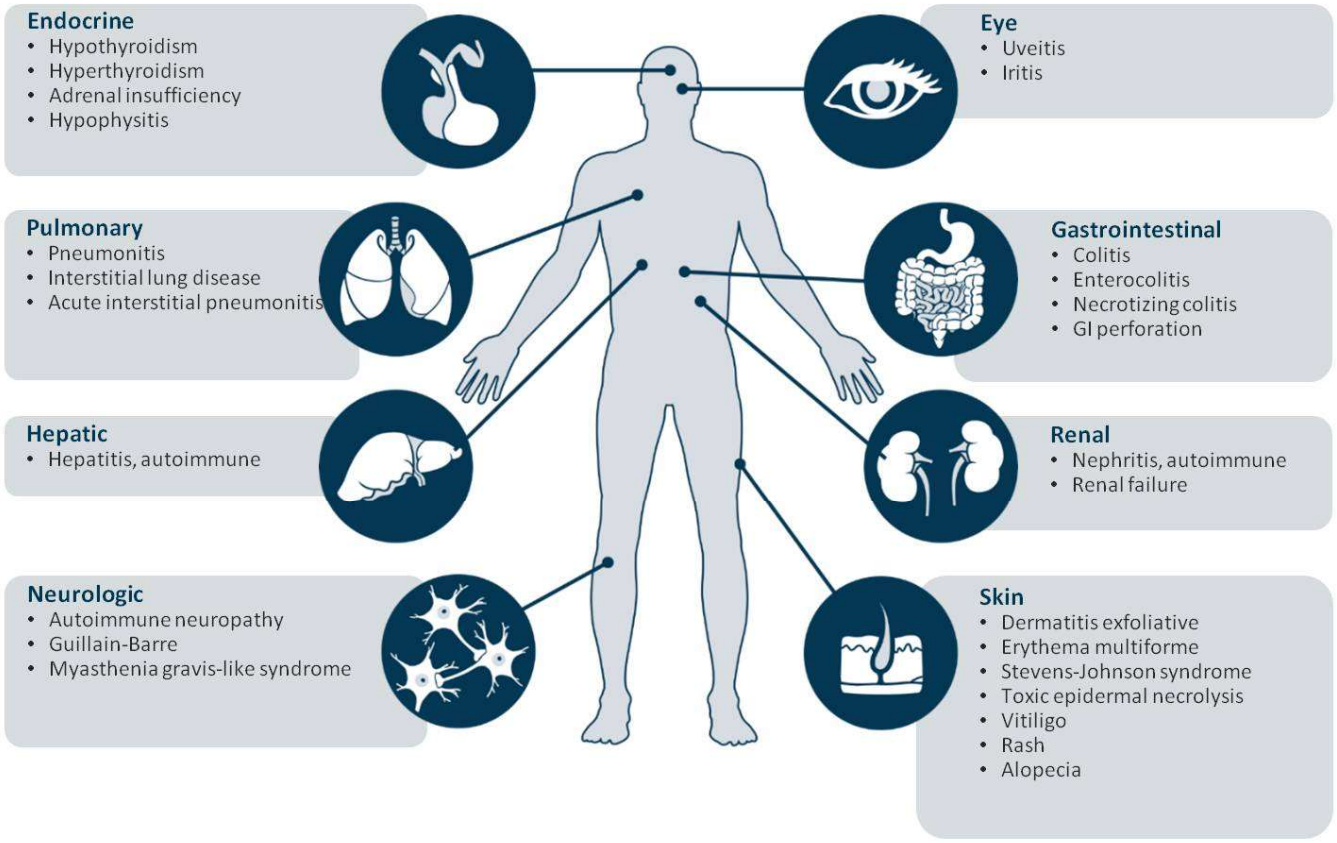
Mount Sinai Comprehensive Cancer Center
Miami Beach, FL

Disclosures

- Speaker's bureau for *Genentech*, *Novartis*, and *Array BioPharma*

Immune-Related Adverse Events

- Result from dysregulation of immunity and tolerance
- Wide spectrum of toxicity



Presented By Jeffrey Weber at 2018 ASCO Annual Meeting

Guidelines

- ESMO
- SITC
- ASCO
- NCCN

Presented By Julie Brahmer at 2018 ASCO Annual Meeting

Key Take Home Points

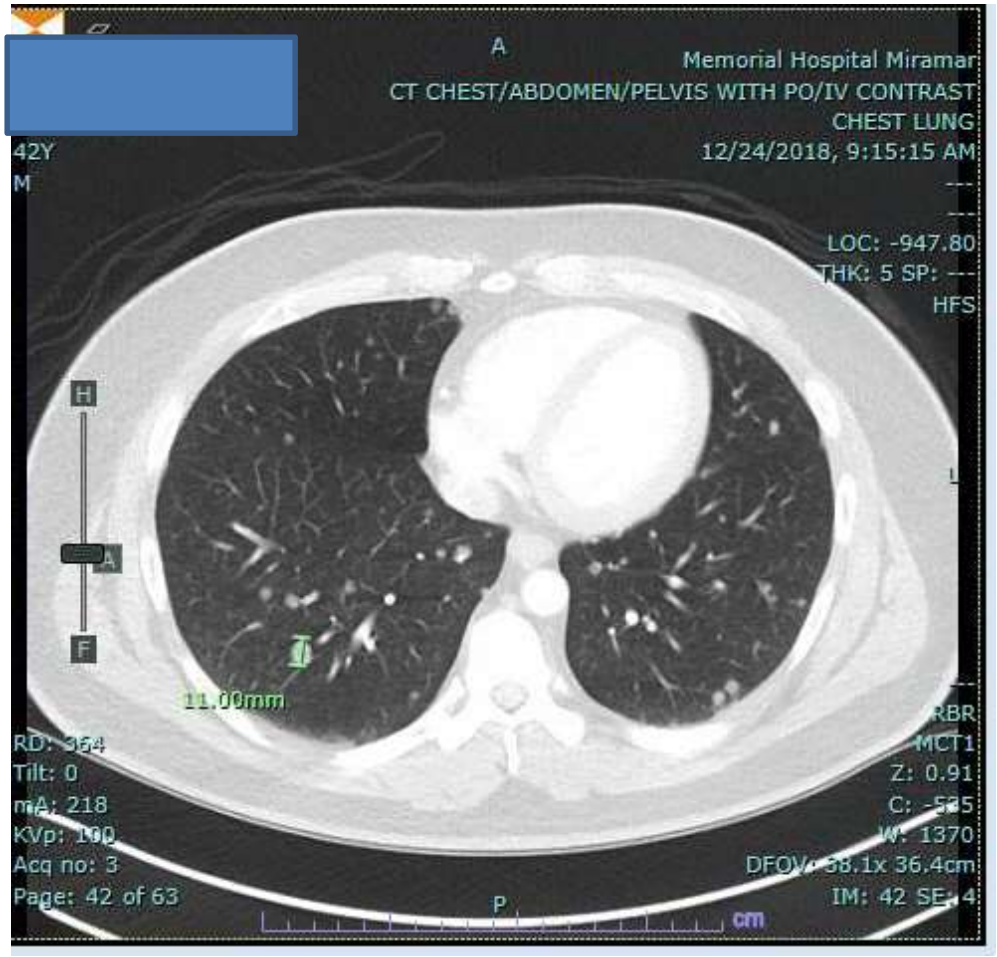
- Immune checkpoint blockade is associated with unique clinical features
  - irAEs → contemporary type of oncologic emergency
    - Can affect any organ system, anytime during therapy
    - Can mimic many other conditions

- ***Early recognition and effective management of irAEs is crucial to optimal use of checkpoint inhibitors***
  - Maintain high index of suspicion
  - Early communication with the entire care team
  - Have your stable of experts available to help you

Case 1
Metastatic Melanoma

- 42 y/o male with stage IV metastatic melanoma to lung and skin.
- He was seen as a new patient for treatment options in Dec 2018; he was treatment naïve.

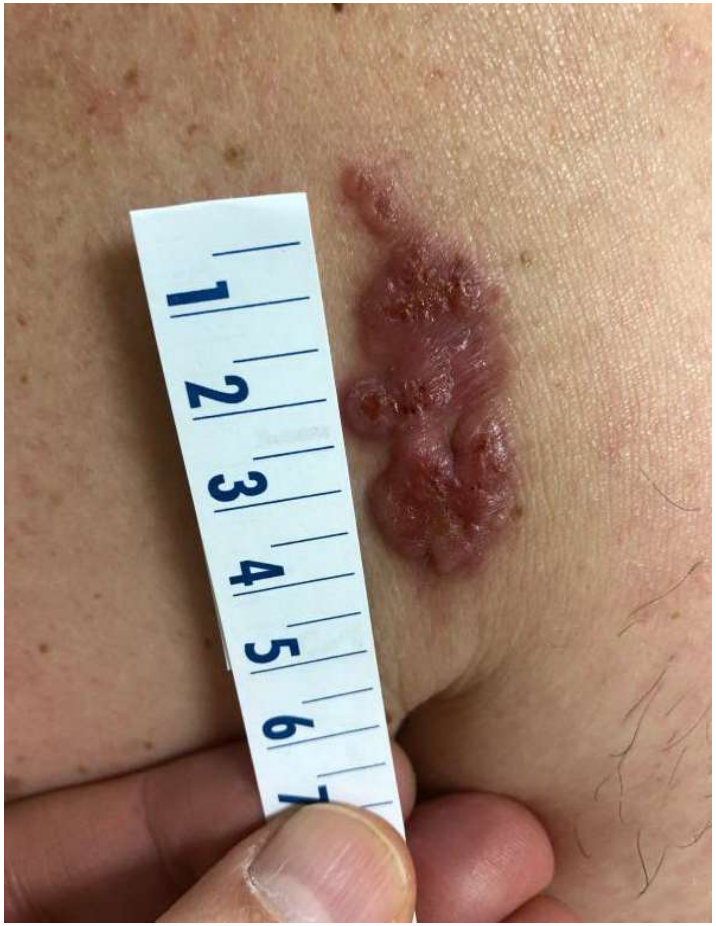
Case 1
Metastatic Melanoma



Pre-treatment CT of chest December 24, 2018

Case 1
Metastatic Melanoma

A.



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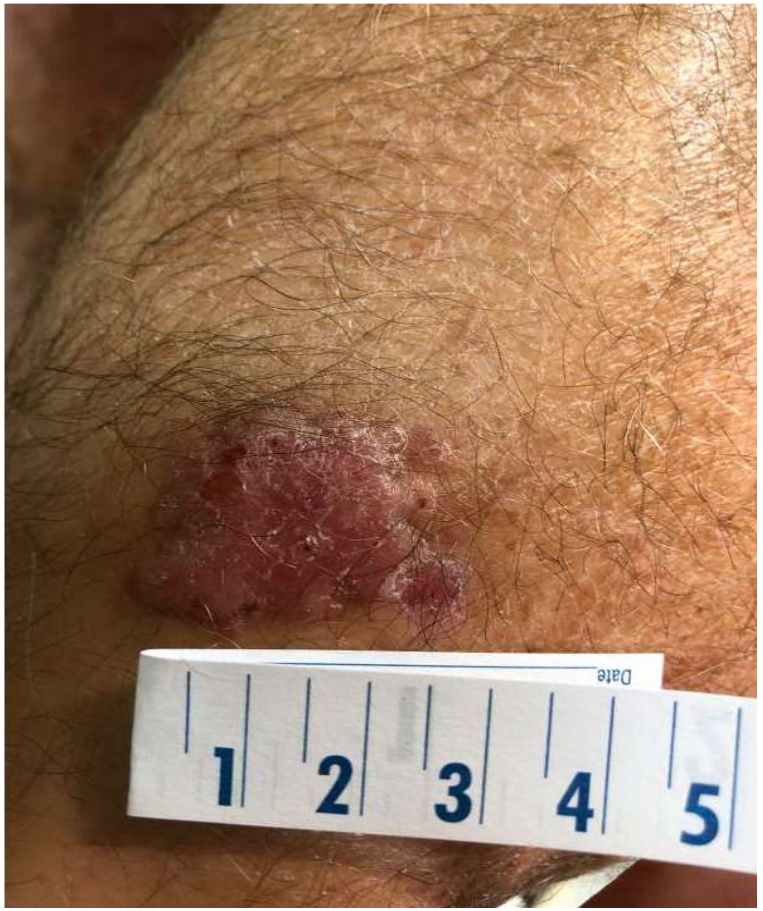
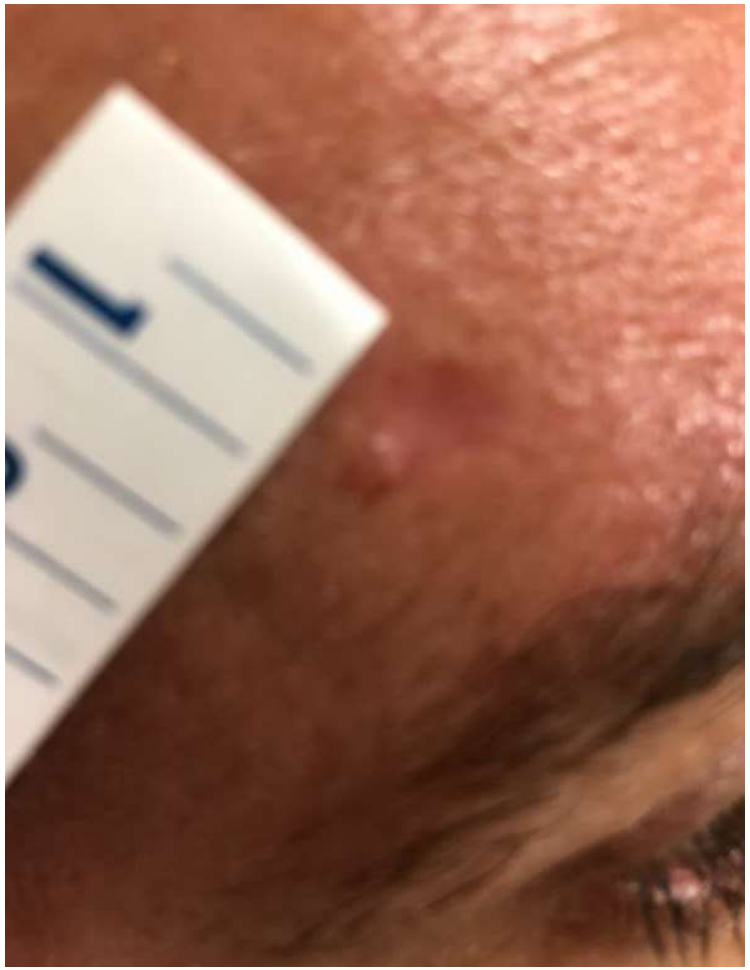


Images from December 18, 2018: A. Right anterior shoulder B. Left elbow C. Right forehead

Case 1
Metastatic Melanoma

C.



Images from December 18, 2018: A. Right anterior shoulder B. Left elbow C. Right forehead

Case 1
Metastatic Melanoma

FOUNDATIONONE®CDx

[redacted]

TUMOR TYPE
Skin melanoma

REPORT DATE
17 Jan 2019

ORF#
078878

PATIENT

DISEASE Skin melanoma

[redacted]

PHYSICIAN

[redacted]

SPECIMEN

SPECIMEN SITE Abdominal wall
SPECIMEN ID SW18-22827 F6
SPECIMEN TYPE Block
DATE OF COLLECTION 21 November 2018
SPECIMEN RECEIVED 03 January 2019

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
BRAF V600E	Cotellic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib) Mekinist® (Trametinib) Tafinlar® (Dabrafenib) Zelboraf® (Vemurafenib)

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §
Tumor Mutational Burden 4 Muts/Mb §
CRKL amplification §
EPHB1 R80W
MDM2 amplification §
TERT promoter -146C>T

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Case 1
Metastatic Melanoma

- He began treatment on ipilimumab (1 mg/kg) + nivolumab (3 mg/kg) on December 26, 2018.
- At 1 week FU, the patient reported grade 1 arthralgias and low grade fever (T max 99.6°F).
- But, also noted slight decrease in the skin lesions.

Case 1
Metastatic Melanoma

- He received cycle 2 of ipilimumab/nivolumab on January 16, 2019.
- 1 week later in FU, the patient again reported that the skin lesions were decreasing, but he reported more AEs including: grade 2 fatigue, grade 1 arthralgias, grade 1 diarrhea, grade 1 fever (T max 101.5°F) and now **CHEST TIGHTNESS and COUGH.**

Case 1
Metastatic Melanoma

- Differential diagnoses:
  - Immune-mediated pneumonitis
  - Pneumonia
  - Disease progression
- Work-up:
  - Preliminary CXR
  - Pulse oximetry (rest and after exertion)- 99% and 95%

Case 1

Metastatic Melanoma

Case 1
Metastatic Melanoma

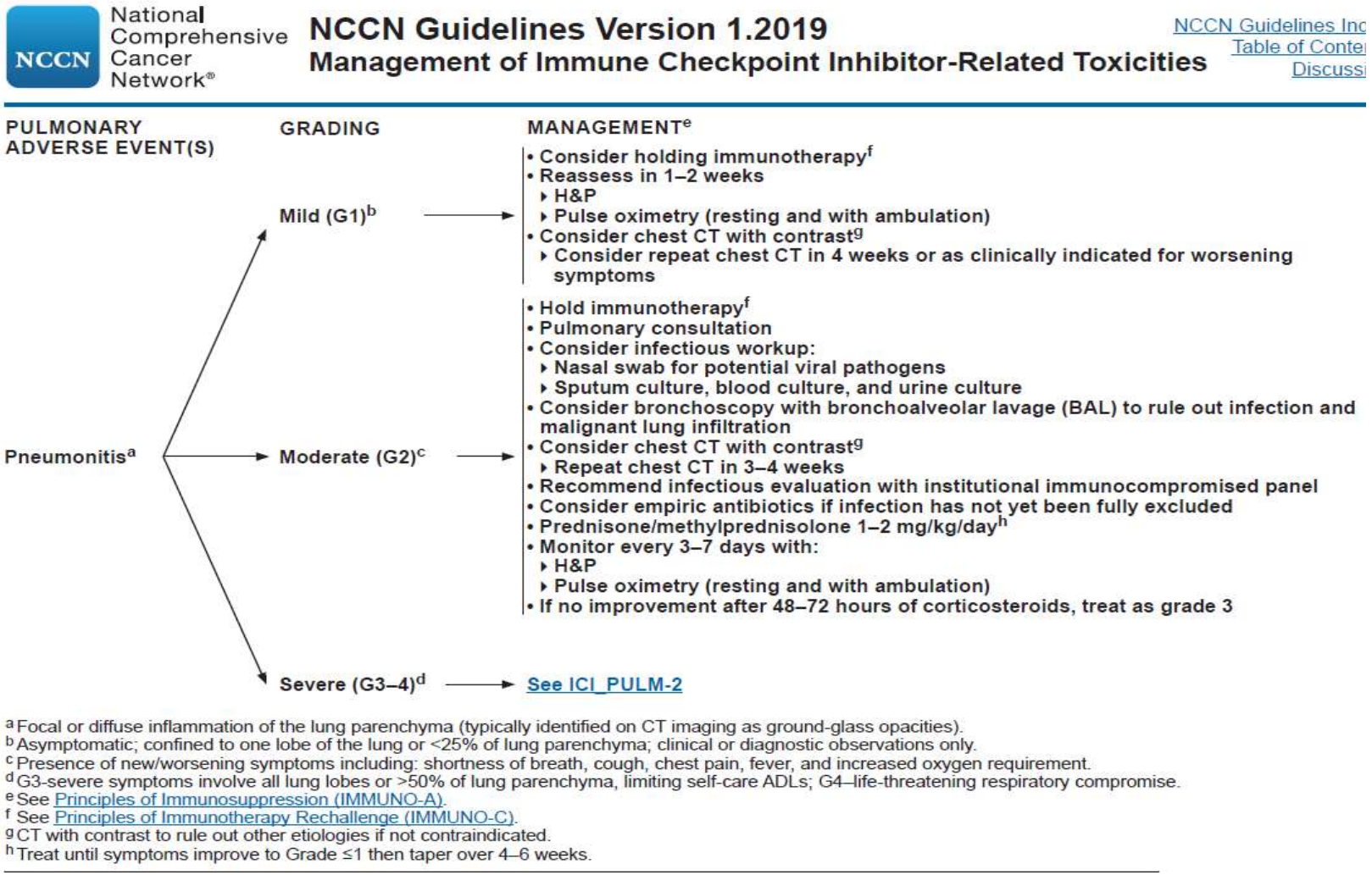
- Treatment:

  -Solumedrol 100 mg IV in clinic

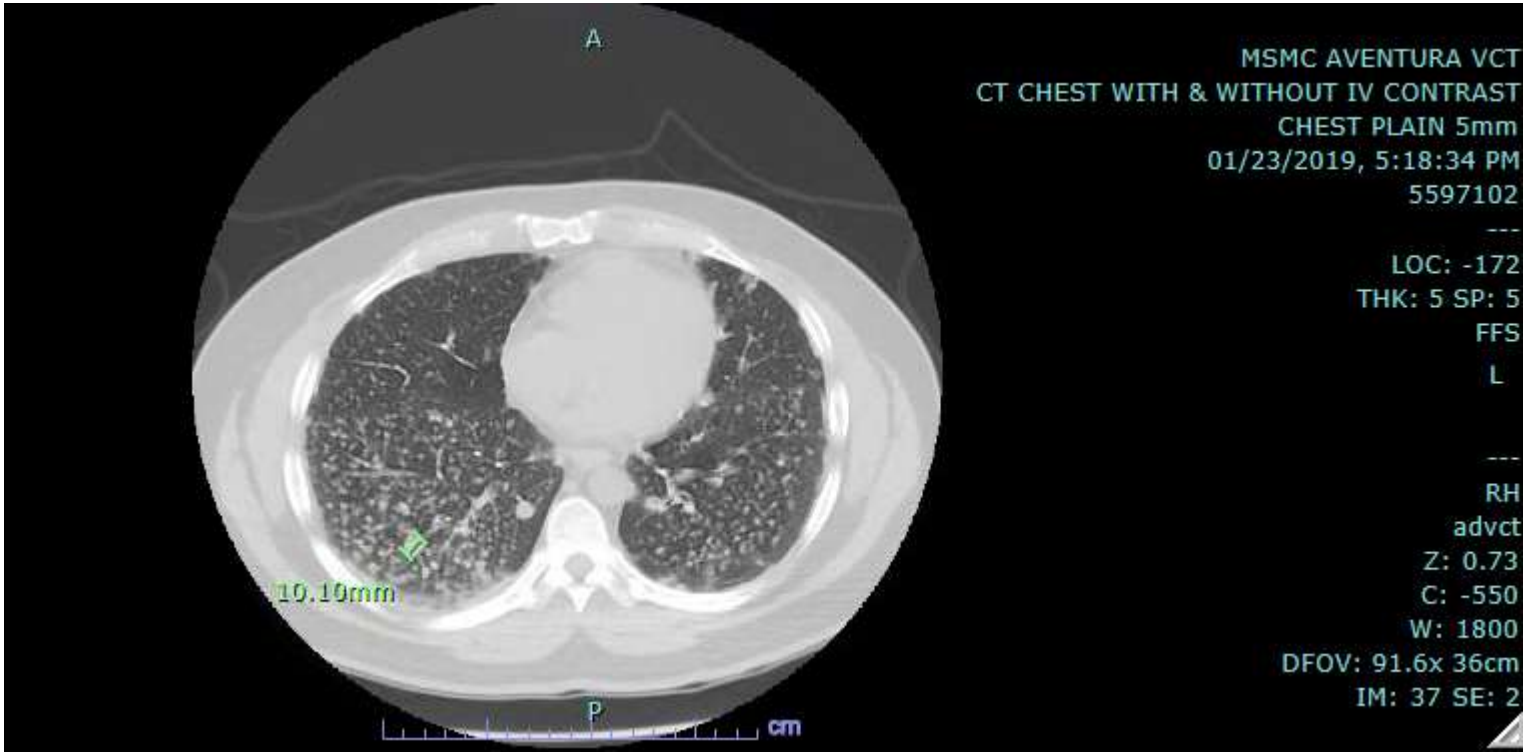
  -Sent home with prednisone 80 mg and Zantac

  -CT of chest and pulmonary evaluation

Case 1
Metastatic Melanoma



Case 1
Metastatic Melanoma

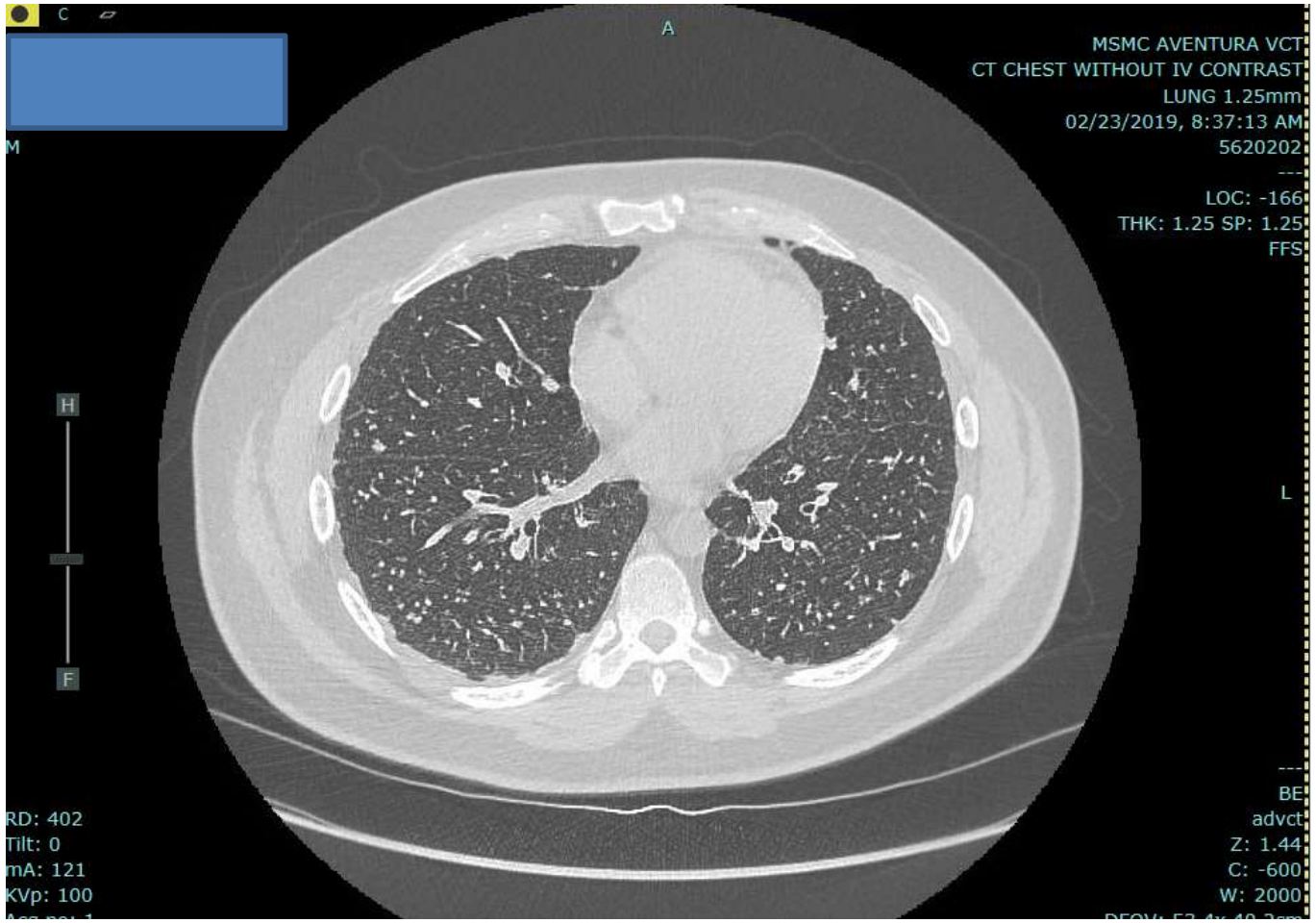


Case 1
Metastatic Melanoma

- Patient was continued on prednisone and steroids tapered.

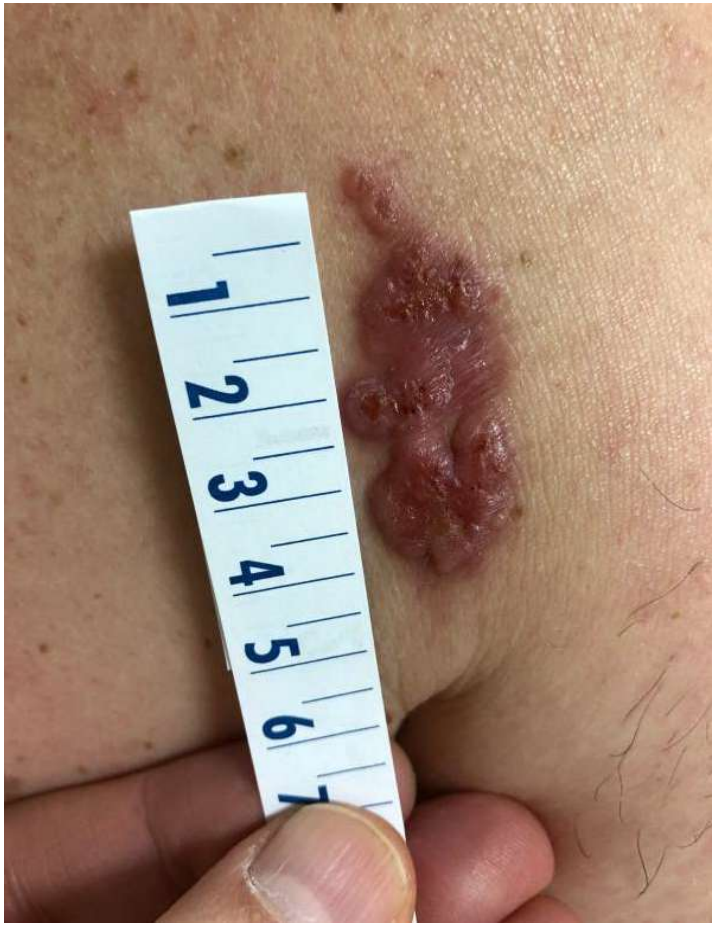
Case 1

Metastatic Melanoma



Case 1
Metastatic Melanoma

A.



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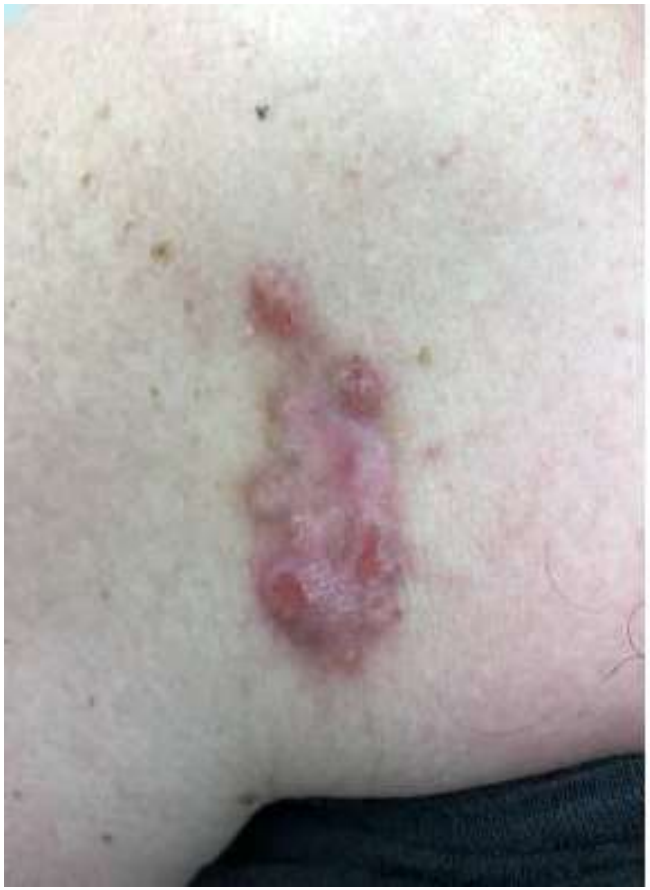
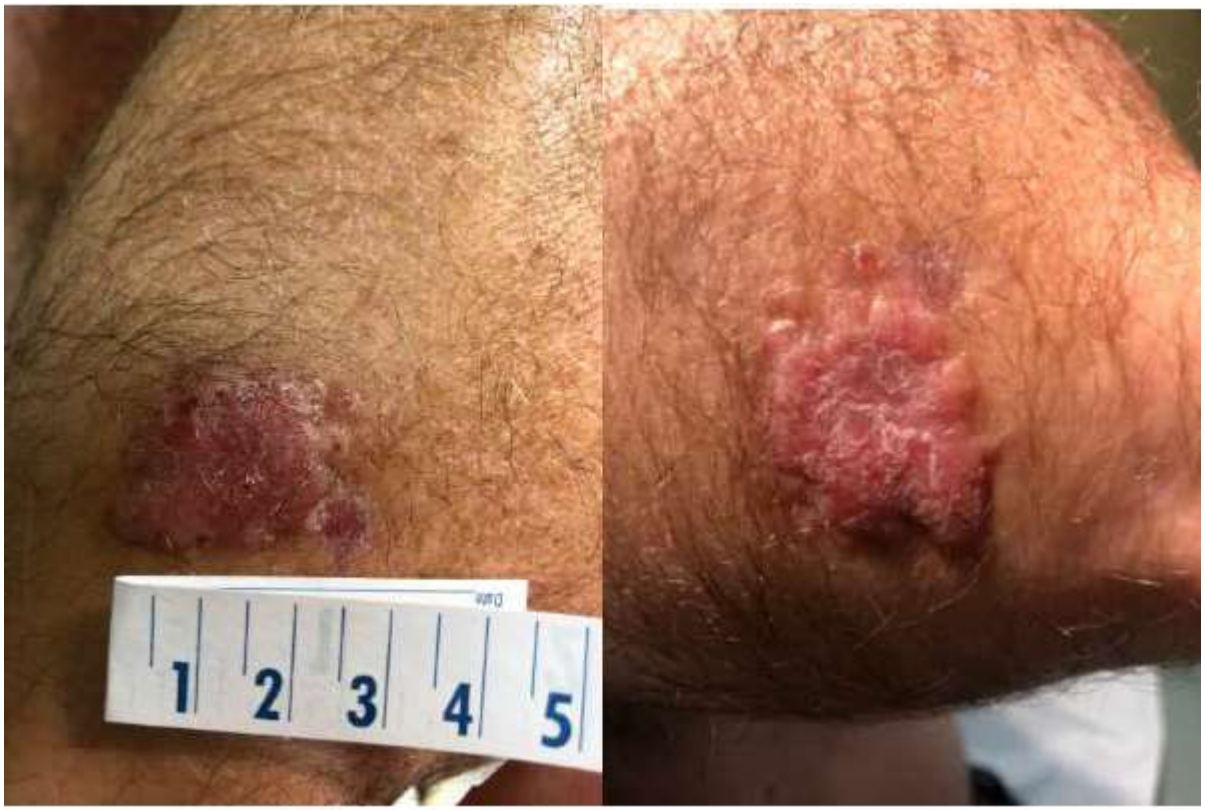


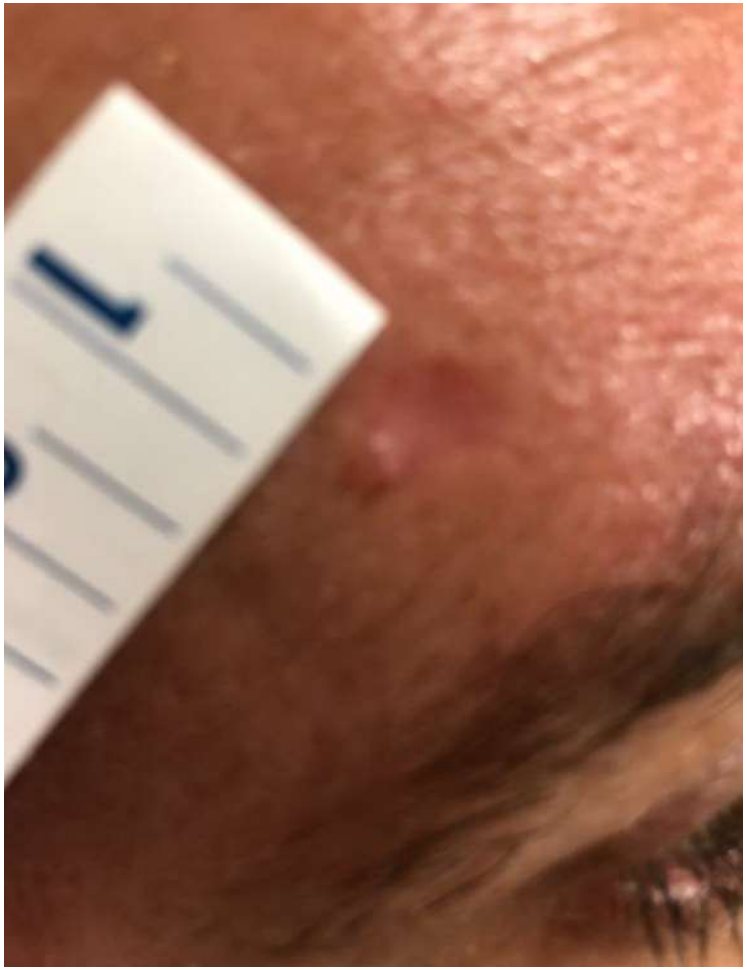
Images of Right ant. Shoulder from December 18, 2018 and February 27, 2019 respectively

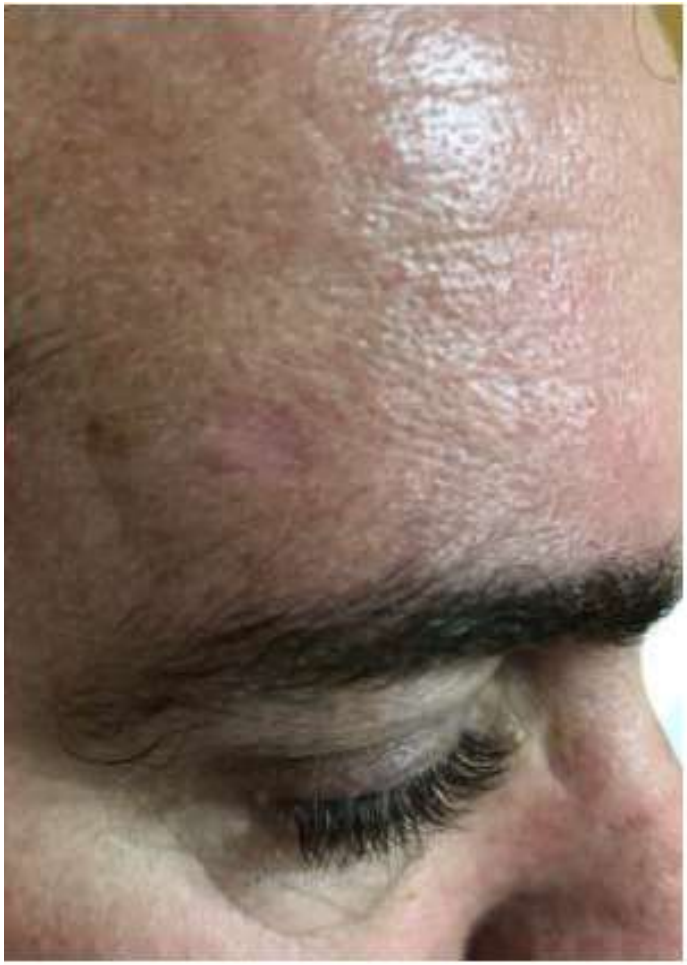
Case 1
Metastatic Melanoma



Images from December 18, 2018 and January 25, 2019 respectively

Case 1
Metastatic Melanoma





*Images from December 18, 2018 and January 25, 2019 respe*ctively

Case 1
Metastatic Melanoma

- Ipilimumab and nivolumab were discontinued (assumed to be progression) and the patient was started on targeted therapy with a BRAF and MEK inhibitor given the BRAF V600+ melanoma.

Case 1
Metastatic Melanoma

- What I learned:

  -Always best to have a systematic approach to managing potential IrAEs even when you have experience.

  -You need your specialists.

  -And after a literature search, there have been cases of marked progression after immunotherapy in patients with MDM2 amplification.

Case 1
Metastatic Melanoma

FOUNDATIONONE®CDx

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Case 1
Metastatic Melanoma

Hyper-progressors after Immunotherapy:

Analysis of Genomic Alterations Associated with Accelerated Growth Rate

Shumei Kato* [1], Aaron Goodman* [1], Vighnesh Walavalkar [2], Donald A. Barkauskas [3], Andrew Sharabi [1,4], Razelle Kurzrock [1]

*Contributed equally

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[2] Department of Pathology,

University of California San Diego Moores Cancer Center

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University of California San Diego Moores Cancer Center

Case 1
Metastatic Melanoma

ABSTRACT

Purpose: Checkpoint inhibitors demonstrate salutary anti-cancer effects including long-term remissions. PD-L1 expression/amplification, high mutational burden and mismatch repair-deficiency correlate with response. We have, however, observed a subset of patients who appear to be "hyper-progressors," with a greatly accelerated rate of tumor growth and clinical deterioration compared to pre-therapy, which was also recently reported by Institut Gustave Roussy. The current study investigated potential genomic markers associated with "hyper-progression" after immunotherapy.

Method: Consecutive stage IV cancer patients who received immunotherapies (CTLA-4, PD-1/PD-L1 inhibitors or other [investigational] agents) and had their tumor evaluated by next-generation sequencing were analyzed (N=155). We defined hyper-progression as time-to-treatment failure (TTF) <2 months, >50% increase in tumor burden compared to pre-immunotherapy imaging, and >

Results: Amongst 155 patient
MDM2/MDM4 amplification
remarkable increases in
accelerated progressi pace (2.5-, 7.1-, 7.2- and 42.5-fold compared to the two months before immunotherapy). In multivariate analysis, *MDM2/MDM4* and *EGFR* alterations correlated with TTF<2 months. Two of 10 patients with *EGFR* alterations were also hyper-progressors (53.6% and 125% increase in tumor size; 35.7- and 41.7-fold increase).

"In a multivariate analysis, MDM2/MDM4 and EGFR alterations correlated with TTF < 2 months".

Conclusion: Some patients with *MDM2* family amplification or *EGFR* aberrations had poor clinical outcome and significantly increased rate of tumor growth after single-agent checkpoint (PD-1/PD-L1) inhibitors. Genomic profiles may help to identify patients at risk for hyper-progression on immunotherapy. Further investigation is urgently needed.

Case 2
Metastatic Melanoma

- 59 y/o female with stage IV melanoma treated initially with neoadjuvant chemo-RT followed by thoracotomy for a misdiagnosed peripheral nerve sheath tumor at another institution, eventually correctly diagnosed as melanoma.
- She was seen as a new patient in February 2018.
- At the time of consultation, the patient had been started on targeted therapy with dabrafenib + trametinib.

Case 2
Metastatic Melanoma

- After 9 months of responding to targeted therapy, the patient progressed with recurrent disease in the right chest wall, liver, and lungs.
- Her targeted therapy was discontinued and the patient was started on combination immunotherapy with ipilimumab 1mg/kg and nivolumab 3 mg/kg on November 21, 2018.

Case 2
Metastatic Melanoma

- On 12/12 visit, patient complained of grade 2 pruritus and grade 1 dry cough.
- Work-up:
  - Preliminary CXR→*no significant findings*
  - Pulse oximetry (rest and after exertion)
- Treatment:

  -Medrol dose pack (to address pruritus and cough).

  -Cycle 2 of ipi/nivo.

Case 2
Metastatic Melanoma

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
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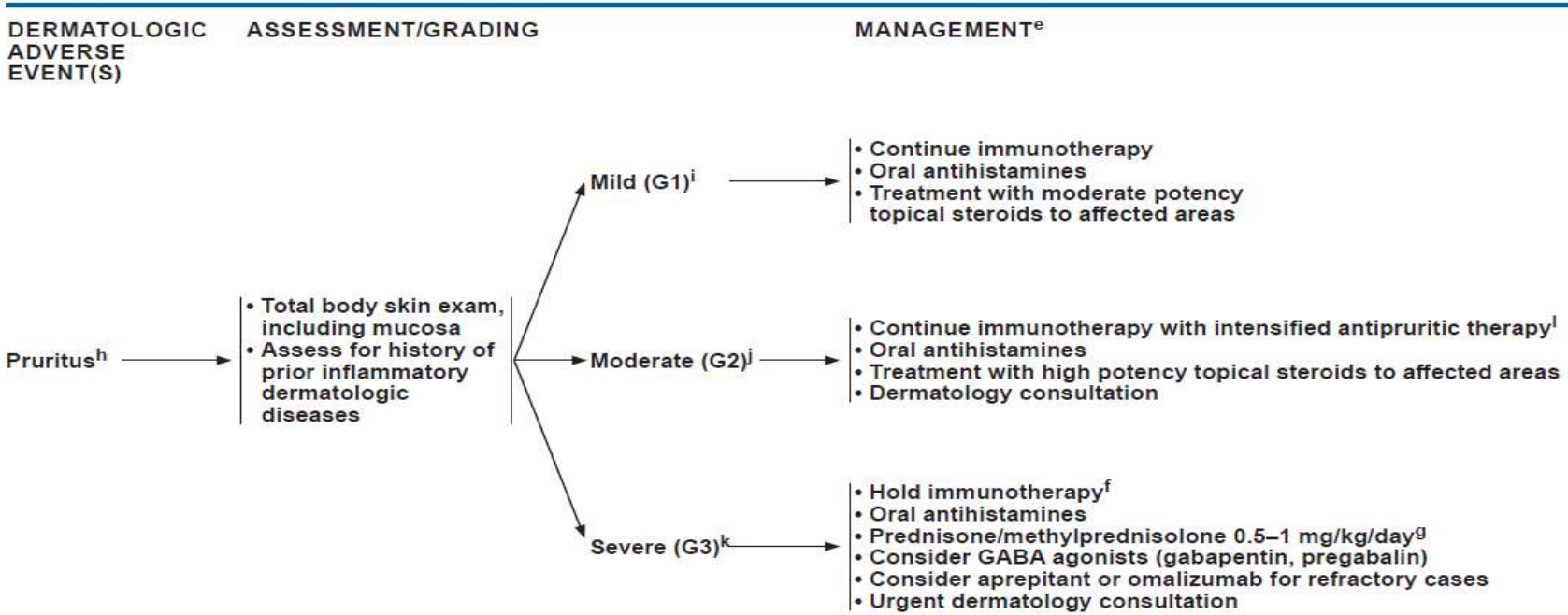
Discussion



[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h] Characterized by an intense itching sensation.
[i] Mild or localized.
[j] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[k] Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE.
[l] Consider holding in select cases.

Case 2
Metastatic Melanoma

- 12/17, patient called stating pruritus worse despite Medrol dose pack and cough unchanged.
- Treatment:

  -Prednisone 20 mg and Doxepin 6mg
- At 12/19 FU, still no relief and cough persists

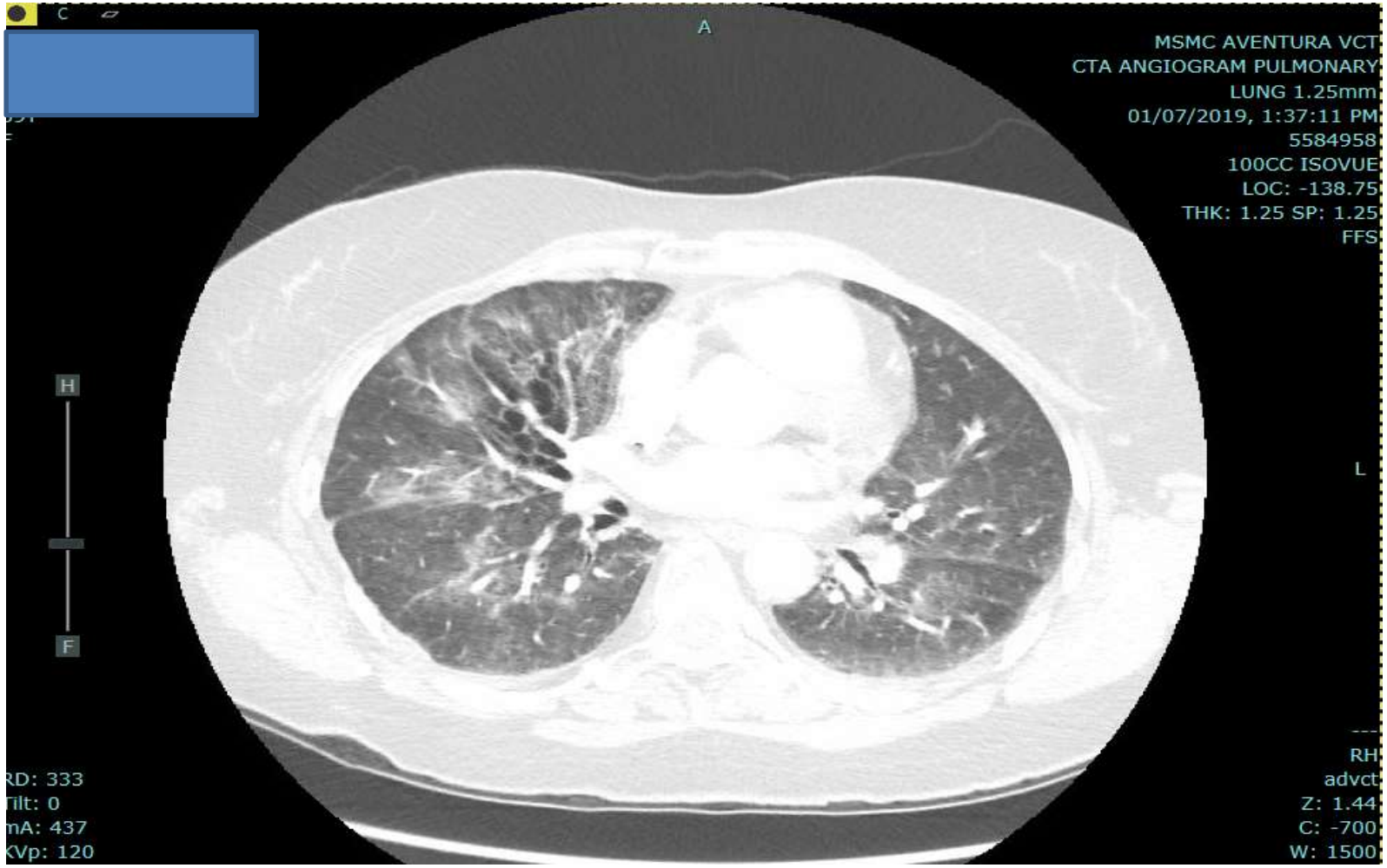
  -Treatment: Solumedrol 40 mg IV in clinic and prednisone 40 mg PO.

Case 2
Metastatic Melanoma

- Pruritus better with doxepin and prednisone 40 mg, but cough now developed into SOB and chest pain.
- While seeing the psychiatrist in clinic on 1/7/2019, she was noted to have obvious SOB and tachypnea.
- Taken to the ED and CT angio demonstrated

Case 2

Metastatic Melanoma



Case 2
Metastatic Melanoma

- She also had elevated troponins and cardiac catherization demonstrated complete occlusion of right coronary artery which was stented. (Echo with preserved EF).
- Patient admitted from 1/7-1/11 followed by 2 week in rehab for steroid myopathy.
- Discharged home on Solumedrol 100 mg BID

Case 2
Metastatic Melanoma

- At office FU on 1/30, patient was still requiring Solumedrol 80 mg BID.
- LFTs demonstrated grade 1 elevation

Case 2

Metastatic Melanoma

Component	Value	Ref Range & Units	Status	Collected	Lab
Sodium	138	136 - 145 MMOL/L	Final	01/30/2019 10:30 AM	LCB
Potassium	4.1	3.5 - 5.1 MMOL/L	Final	01/30/2019 10:30 AM	LCB
Chloride	101	98 - 107 MMOL/L	Final	01/30/2019 10:30 AM	LCB
CO2	29.7	21.0 - 32.0 MMOL/L	Final	01/30/2019 10:30 AM	LCB
Glucose	120 ^	74 - 106 MG/DL	Final	01/30/2019 10:30 AM	LCB
BUN	19.0 ^	7.0 - 18.0 MG/DL	Final	01/30/2019 10:30 AM	LCB
Creatinine	0.77	0.55 - 1.02 MG/DL	Final	01/30/2019 10:30 AM	LCB
Calcium	8.7	8.5 - 10.1 MG/DL	Final	01/30/2019 10:30 AM	LCB
AST (SGOT)	40.0 ^	15.0 - 37.0 U/L	Final	01/30/2019 10:30 AM	LCB
ALT (SGPT)	112.0 ^	13.0 - 56.0 U/L	Final	01/30/2019 10:30 AM	LCB
Protein, Total	6.5	6.4 - 8.2 G/DL	Final	01/30/2019 10:30 AM	LCB
Albumin	3.4	3.4 - 5.0 G/DL	Final	01/30/2019 10:30 AM	LCB

Case 2
Metastatic Melanoma

- But on 2/13 FU, while on Solumedrol 50 mg BID, LFTs markedly increased.

Case 2

Metastatic Melanoma

Component Results

Component	Value	Ref Range & Units	Status	Collected
Sodium	137	136 - 145 MMOL/L	Final	02/13/2019 1:43 PM
Potassium	3.7	3.5 - 5.1 MMOL/L	Final	02/13/2019 1:43 PM
Chloride	100	98 - 107 MMOL/L	Final	02/13/2019 1:43 PM
CO2	28.8	21.0 - 32.0 MMOL/L	Final	02/13/2019 1:43 PM
Glucose	147 ^	74 - 106 MG/DL	Final	02/13/2019 1:43 PM
BUN	14.0	7.0 - 18.0 MG/DL	Final	02/13/2019 1:43 PM
Creatinine	0.71	0.55 - 1.02 MG/DL	Final	02/13/2019 1:43 PM
Calcium	9.0	8.5 - 10.1 MG/DL	Final	02/13/2019 1:43 PM
AST (SGOT)	479.0 ^	15.0 - 37.0 U/L	Final	02/13/2019 1:43 PM
ALT (SGPT)	1,631.0 ^^	13.0 - 56.0 U/L	Final	02/13/2019 1:43 PM
NOTIFIED DIE[redacted]448 BY RM				
Protein, Total	7.2	6.4 - 8.2 G/DL	Final	02/13/2019 1:43 PM
Albumin	3.2 v	3.4 - 5.0 G/DL	Final	02/13/2019 1:43 PM
Globulin	4.0 ^	2.3 - 3.5 G/DL	Final	02/13/2019 1:43 PM
Alkaline Phosphatase	259 ^	46 - 116 U/L	Final	02/13/2019 1:43 PM
Bilirubin, Total	1.64 ^	0.20 - 1.00 MG/DL	Final	02/13/2019 1:43 PM
Anion Gap	11.9	10.0 - 20.0 MMOL/L	Final	02/13/2019 1:43 PM
BUN/Creatinine Ratio	19.7	8.0 - 30.0	Final	02/13/2019 1:43 PM
Albumin/Globulin Ratio	0.8 v	1.0 - 2.5	Final	02/13/2019 1:43 PM
Calculated Osmolality	277	275 - 295 MOSM/KG	Final	02/13/2019 1:43 PM
EGFR	>60	>60 mL/min/1.73m2	Final	02/13/2019 1:43 PM

If patient is African American, please multiply this result by 1.212.

Case 2
Metastatic Melanoma

- The patient was readmitted, steroids continued but at higher doses, mycophenolate started, and viral etiology ruled out.
- After a 12 day admission, the patient was discharged home. Now on prednisone 40 mg BID and remains on mycophenolate 1 gm BID.
- As of 3/6, pneumonitis grade 1, LFTS still with grade 3 elevation but markedly decreased with an of ALT and AST of 668 U/L and 153 U/L respectively.

Case 2
Metastatic Melanoma

- Unfortunately, earlier that morning, the patient heard a “crack” in her back followed by severe back pain.
- And so the saga continues…

Case 2
Metastatic Melanoma

What I learned from this case:

- Don’t be afraid to give high doses of corticosteroids but taper slowly.
- If corticosteroids don’t work quickly, add another immunosuppressant.
- Hospital admission may be necessary if outpatient management not sufficient.
- One can develop more than one toxicity sequentially or concomitantly
- There are some tumors that are histologically similar and mutation analysis and NGS may help making a proper diagnosis.

Case 3

Metastatic Melanoma

- 79 year old female with a history of irritable bowel syndrome, colon cancer requiring colectomy, resection at anastomotic site from ulceration, and severe rheumatoid arthritis requiring 7 years of immunosuppressive therapy with Humira and Enbrel.
- She initially presented with a stage IIIB melanoma but developed metastatic disease to lung.
- BRAF V600 mutation was negative.

Case 3
Metastatic Melanoma

- Because of limited treatment options, the patient agreed to a trial of pembrolizumab.
- After cycle 1 of pembrolizumab, the patient developed grade 3 diarrhea.
- What next?
- Patient instructed to take prednisone 60 mg and come to clinic immediately.

Case 3

Metastatic Melanoma

- Differential diagnosis:
  - Infectious colitis
  - Immune-mediated diarrhea/colitis
- The following day in clinic, she had a grade 1 diarrhea
- Work-up:
  - Stool sample: O&P, Culture, C. Difficile toxin, WBC
  - Consider colonoscopy
- Treatment:

  -Patient instructed to taper prednisone

Case 3
Metastatic Melanoma

- Infectious workup negative.
- Do we rechallenge patient with immunotherapy?
- We did. And she never redeveloped diarrhea.
- In addition, she had a complete response after 1 year of therapy.

Case 3

Metastatic Melanoma

Table. Understanding Flares of Autoimmune Disease (AI) or Prior Immune-Related AEs During Treatment With Checkpoint Inhibition

Study [Reference]	Drug Target	Number of Patients	Patient Population	ORR	Flares	irAEs	Treatment for Flares
Kyi et al [12]	CTLA-4	2	AI	50%	1/2 flare of prior AI	Arthritis	Celecoxib
Johnson et al [14]	CTLA-4	30	AI	20%	27%	Hypophysitis, colitis	Corticosteroids (10), infliximab (2); 1 death
Lee et al [15]	CTLA-4	8	AI	57%	62.5%	50% colitis, 50% flare of prior arthritis	5/8 flares required discontinuation of drug
Menzies et al [18]	PD-1	119	52 with preexisiting AI	33%	38%	Arthritis, dermatologic	Corticosteroids (14%), permanent discontinuation of anti–PD-1 (8%)
			67 with prior CTLA-4–related AEs	40%	3% flares of prior CTLA-4–related AEs, 34% distinct irAEs	Colitis, hepatitis, pneumonitis	Corticosteroids (21%), steroid-sparing agents (4%), discontinuation of anti–PD-1 (12%)
Bender et al [19]	PD-1	10	Prior CTLA-4–related AEs	NA	10% distinct irAEs	Pancreatitis	Corticosteroids, mycophenolate mofetil
Pollack et al [20]	PD-1	80	Prior CTLA-4 + PD-1 combination irAEs	70%	18% recurrent irAEs, 21% distinct irAEs	Colitis less likely than other irAEs	NA
Gutzmer et al [21]	PD-1	41	19 with AI	32%	42% flares of prior AI, 16% distinct irAEs	Pneumonitis, hypophysitis	Corticosteroids
			22 with prior CTLA-4–related AEs	45%	4.5% flares of prior ipi-related AEs, 23% distinct irAEs	Pancreatitis, arthralgias	Corticosteroids
Danlos et al [22]	PD-1/PD-L1	45	AI	35%	55% flares of prior AI, 22% distinct irAEs	Thyroiditis, colitis	Corticosteroids (13%), discontinuation (8%)

AE = adverse event; CTLA-4 = cytotoxic T-lymphocyte–associated antigen 4; ipi = ipilimumab; irAE = immune-related adverse event; NA = not available; ORR = objective response rate; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1.

Johnson, D et al.

Key Questions about the use of Checkpoint Blockade in Cancer:

- Can you re-start immunotherapy after a grade 3-4 irAE?
- Yes, based on the available literature; Menzies, A et al studied patients with autoimmune disease and those who had prior dose-limiting side effects of checkpoint inhibitors who were subsequently re-treated.
- The rate of subsequent dose-limiting side effects was only about 30%
- Judiciously, one can re-treat patients after complete resolution of grade 3-4 irAEs, using PD-1 antibody alone

Thank you