sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Identification and Management of Immune-Related Adverse Events in the Emergency Setting

Ani Aydin, MD, FAAEM
Assistant Professor
Department of Emergency Medicine
Yale University School of Medicine

Disclosures

- No financial disclosures

ADVANCES IN Cancer IMMUNOTHERAPY™

Mechanism CTLA-4 & PD-1

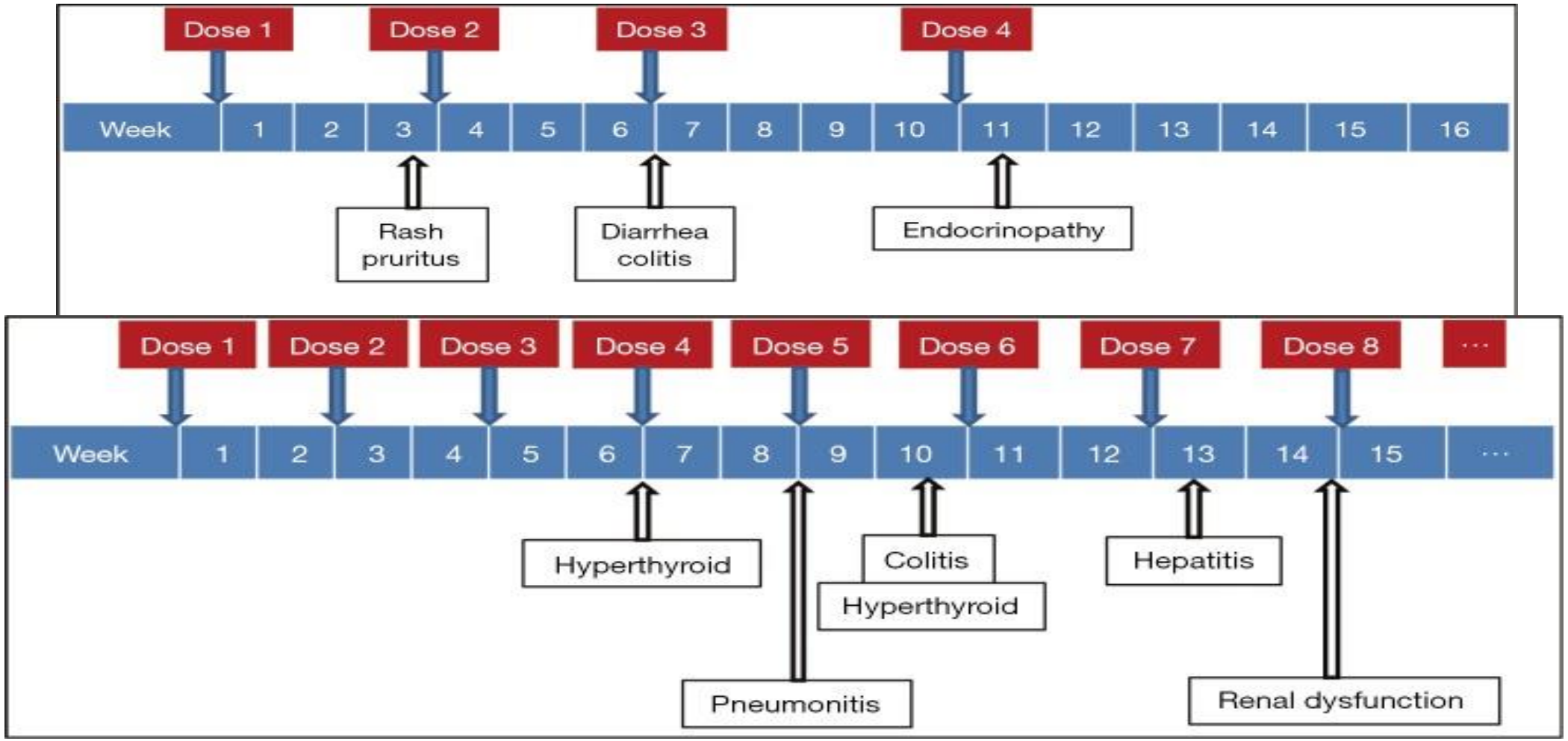
- Involved in maintaining appropriate immune response
- Downregulates & prevents inappropriate activity
- Autoimmune type response
  - Thinking “Chemo” will lead down wrong path
  - **Think Graft versus Host disease**

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Timing

- Most occur within first 3 months
- May occur after final dose
- Some dose dependent
- Grade 3-4 toxicity - 10% overall



ADVANCES IN Cancer IMMUNOTHERAPY™

Dermatologic Toxicity

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Dermatologic Toxicity

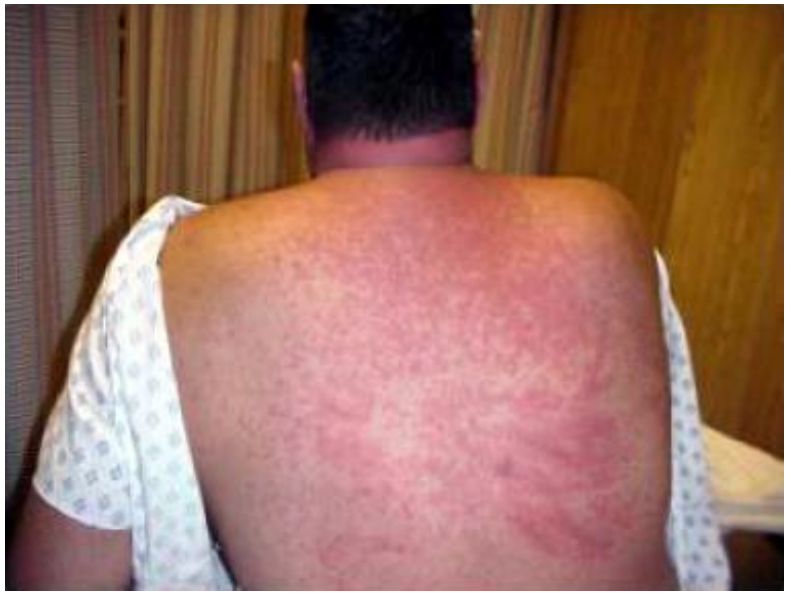
- Presents three weeks into therapy
- **Mild**
  - Maculopapular rash
  - With or without symptoms
    - Pruritus, burning, tightness
  - 10%-30% TBSA
  - Limiting ADL's
  - Topical steroids, hydroxyzine, diphenhydramine
- **Moderate**
  - Diffuse, non-localizing rash
  - 30-50% TBSA
  - Topical corticosteroids, hydroxyzine, diphenhydramine
  - Consider systemic corticosteroids if no improvement in one week (0.5-1mg/kg/day)

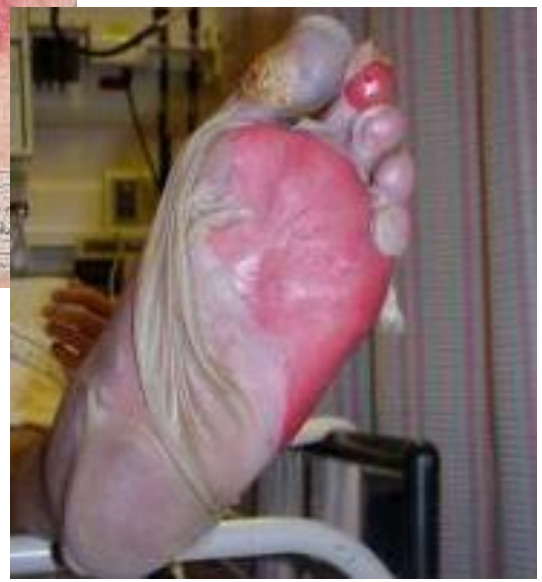
Dermatologic Toxicity

- **Severe**
  - Blisters, dermal ulceration, necrotic, bullous or hemorrhagic
  - Systemic corticosteroids 1-2 mg/kg/day prednisone equivalent
  - Taper over one month following improvement

ADVANCES IN Cancer IMMUNOTHERAPY™

Stevens Johnsons Syndrome (SJS)
TEN (Toxic Epidermal Necrolysis)





Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Dermatologic Toxicity

- **Vitiligo**
  - Most cases permanent
  - No treatment
  - Intra-oral lesions – consider candidiasis

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Vitiligo

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Patient 1

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

- PMH:
  - Small cell lung cancer
  - Hypertension
  - Diabetes

- Meds:
  - Nivolumab

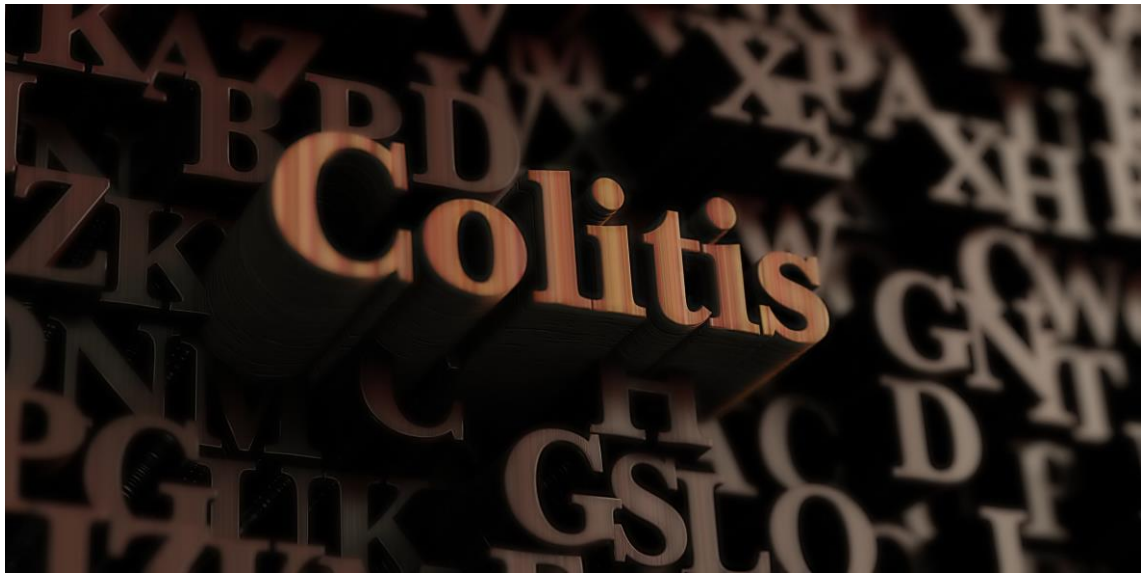
ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Management

- Evaluation
  - Stool studies
  - CT imaging
- Treatment
  - Hydration
  - Anagelsia, anti-emetics
  - Antibiotics
  - Steroids



ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Diarrhea / Colitis

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Diarrhea / Colitis

- **Mild**
  - ≤ 4 stools above baseline/day
  - Testing
    - C-diff, lactoferrin, O&P, stool cultures
  - Treatment
    - Symptomatic: oral hydration & bland diet
    - No corticosteroids
    - Avoid antidiarrheal medications

Diarrhea / Colitis

- **Moderate**
  - 4-6 stools above daily baseline
  - Symptoms
    - Abdominal pain, blood or mucus in stool
  - Testing
    - C-diff, lactoferrin, O&P, stool cultures
  - Systemic corticosteroids
    - 0.5mg/kg/day prednisone equivalent if symptoms > one week

ADVANCES IN Cancer IMMUNOTHERAPY™

Diarrhea / Colitis

- **Severe**
  - ≥ 7 stools above daily baseline
  - Symptoms
    - Peritoneal abdomen
    - Ileus
    - Fever
  - Testing
    - Stool studies
    - Rule out perforation
  - Admission

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Diarrhea / Colitis

- **Severe**
  - Consider empiric antibiotics for fever or leukocytosis
  - Systemic corticosteroids - 1-2mg/kg/day equivalent, if no perforation
    - Hold if clinically stable until stool studies available (24hrs)
    - Unstable – high dose corticosteroids: methylprednisolone 125 mg IV daily x 3 days to evaluate responsiveness
  - Other
    - Infliximab 5 mg/kg if no response to corticosteroids
    - Consider mycophenolate mofetil for select patients

ADVANCES IN Cancer IMMUNOTHERAPY™

Hepatotoxicity

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Hepatotoxicity

- 8-12 weeks after therapy initiation
- Avoid alcohol and acetaminophen

Hepatotoxicity

Grade 2 toxicity

- 2.5 < AST/ALT < 5 times normal
- 1.5 < Bilirubin < 3 times normal
- Corticosteroids 0.5-1 mg/kg/day, 1 month taper

Grade ≥ 3 toxicity

- Admission
- Methylprednisolone IV 125mg/day
- Consider mycophenolate mofetil 500mg PO Q12hrs

ADVANCES IN Cancer IMMUNOTHERAPY™

Endocrinopathies

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Endocrinopathies

- 6 weeks after the initiation of therapy
- Rare
  - <10%
- Both CTLA &PD-1 inhibitors
- Dose dependent

ADVANCES IN Cancer IMMUNOTHERAPY™

Endocrinopathies

- **Hypothyroidism**
  - 1 wk to 19 months after onset of therapy
  - Appropriate levothyroxine replacement
- **Hyperthyroidism**
  - Acute thyroiditis secondary to immune activation
    - Corticosteroids 1 mg/kg for symptomatic patients
- **Adrenal Insufficiency**
  - Admission
  - Corticosteroids 60-80 mg prednisone or equivalent

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Endocrinopathies

- **Hypophysitis**
  - 1-2 months after initiation of therapy
  - Fatigue, headaches, visual field defects
  - ACTH, TSH, FSH, LH, GH, prolactin
  - Imaging – enlarge pituitary gland
  - Steroids
    - Corticosteroids 1 mg/kg/day
    - Dexamethasone 6 mg IV Q6hr x 3 days
    - Methylprednisolone 125 mg IV daily

ADVANCES IN Cancer IMMUNOTHERAPY™

Pneumonitis

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Pneumonitis

- 5 months after treatment initiation
- Occur with CTLA-4 & PD1 inhibitors
- New cough or dyspnea
- Multiple grades

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

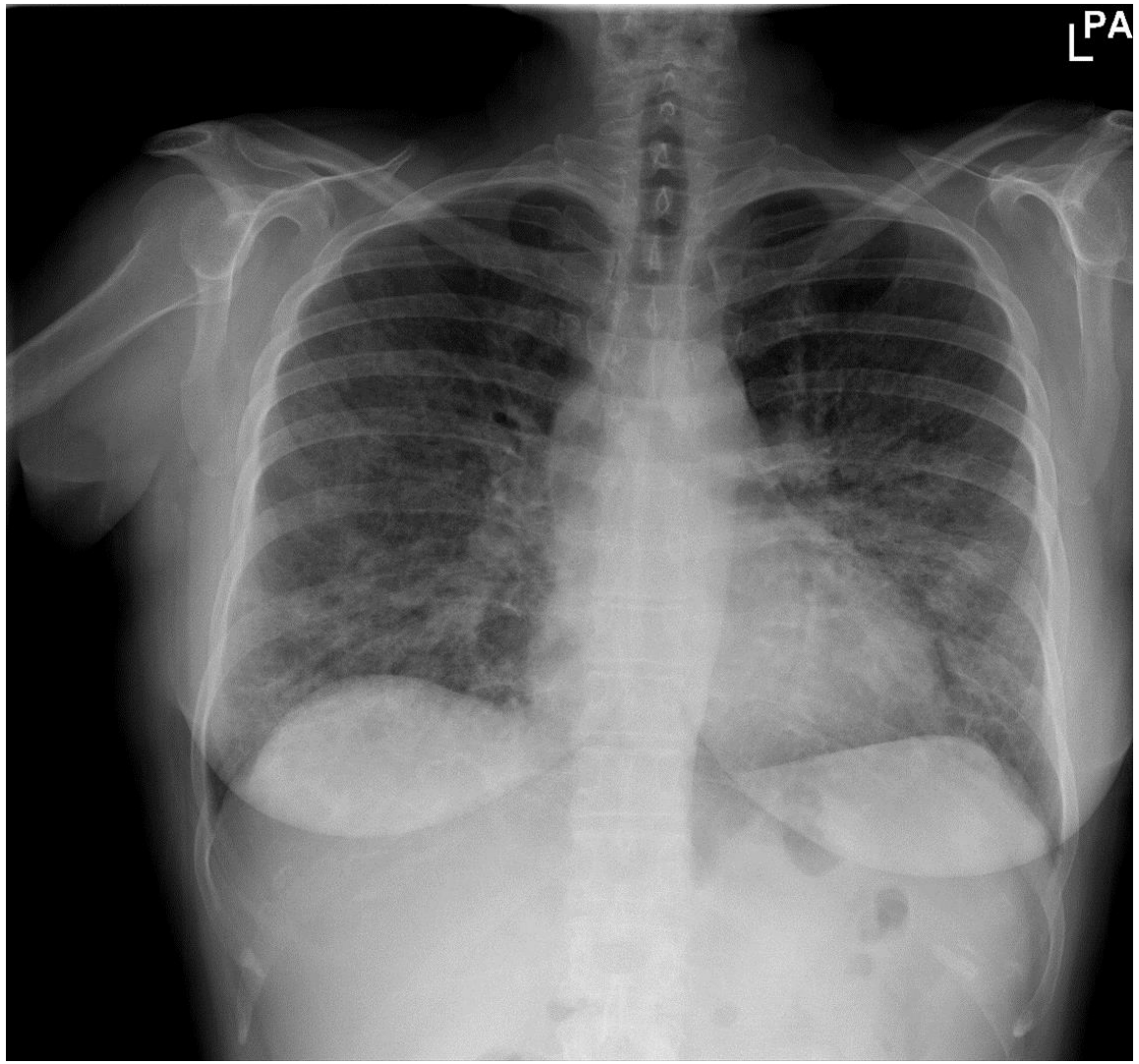
ADVANCES IN Cancer IMMUNOTHERAPY™

Pneumonitis

- Grade 2
  - Admission
  - Prednisone/prednisolone
    - Taper over one month after improvement seen
- Grade 3-4
  - Admission
  - Prednisone/prednisolone
  - Six week taper

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer



ADVANCES IN Cancer IMMUNOTHERAPY™

Pancreatitis

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Pancreatitis

- Elevation amylase & lipase
  - With both CTLA-4 & PD1 inhibitors
  - Without overt pancreatitis
    - Monitor
  - Grade 3-4 with symptoms
    - Hold immunotherapy

- New onset diabetes with DKA
  - Aggressive treatment of DKA
  - With severe disease, consider steroids for adrenal insufficiency

ADVANCES IN Cancer IMMUNOTHERAPY™

Patient 2

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Renal Insufficiency

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Renal Insufficiency

- 10-12 months after initiation of treatment
- Rare, < 1%
- Grade 1: up to 1.5 times above baseline
- Grade 2 to 3: 1.5-6 times baseline
  - Full recovery with high dose corticosteroids (>40 mg/day)

ADVANCES IN Cancer IMMUNOTHERAPY™

Ophthalmologic

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

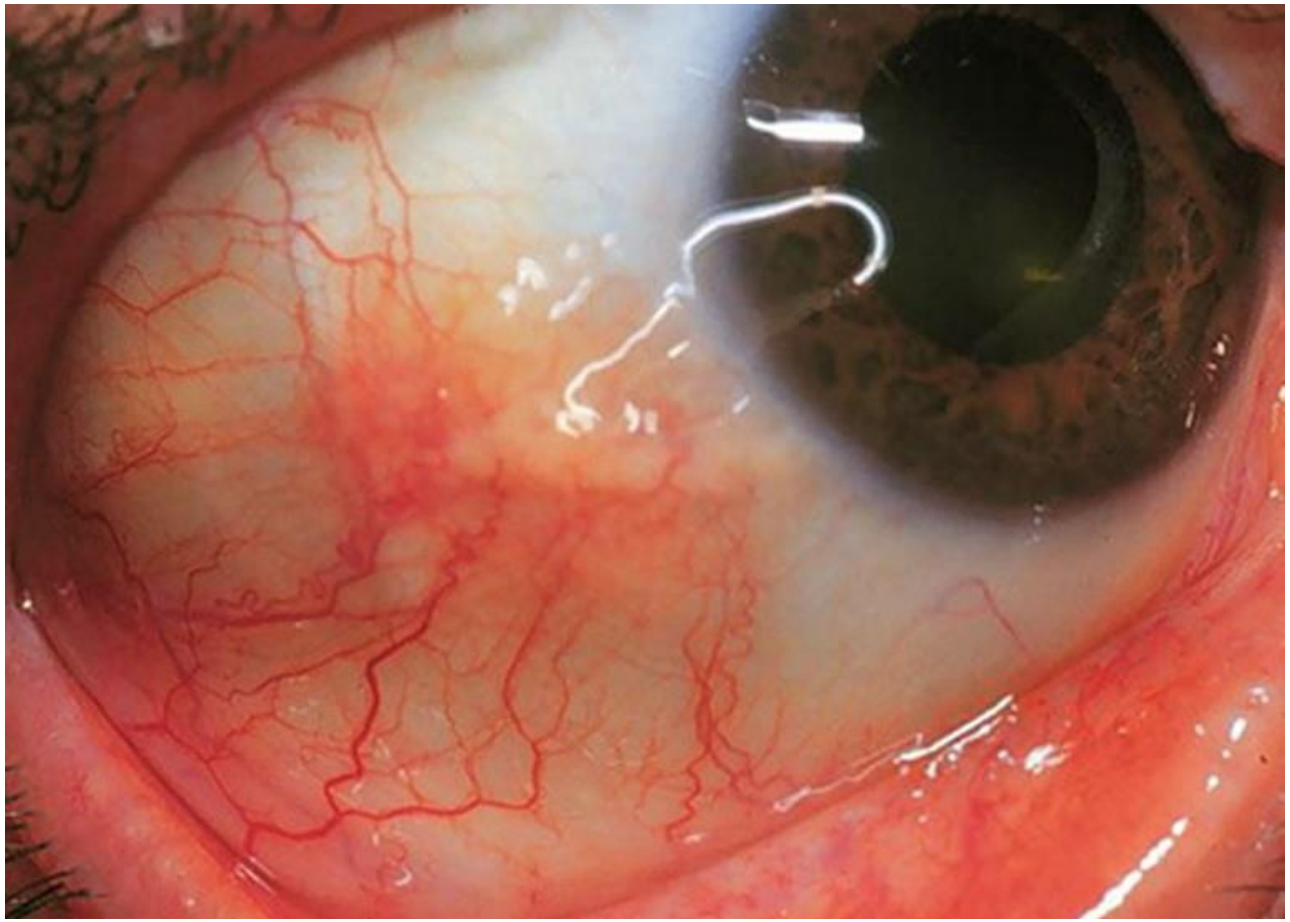
ADVANCES IN Cancer IMMUNOTHERAPY™

Ophthalmologic

- Rare, <1%
- Episcleritis

Association of Community Cancer Centers

Society for Immunotherapy of Cancer



ADVANCES IN Cancer IMMUNOTHERAPY™

Ophthalmologic

- Rare, <1%
- Episcleritis
- Scleritis

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Ophthalmologic

- Rare, <1%
- Episcleritis
- Scleritis
- Conjunctivitis

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Rare irAEs

- <1%
  - Red cell aplasia
  - Thrombocytopenia
  - Hemophilia A
  - Gullian-Barre syndrome
  - Myasthenia gravis
  - Posterior reversible encephalopathy syndrome
  - Aseptic meningitis
  - Transverse myelitis
  - ??

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Patient 3

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

54-year-old male with NSCLC

- New immunotherapy 8 weeks ago for lung cancer

- Painless blurry vision
- Mild HA

- Exam
  - 20/25 right eye (OD), 20/125 left eye (OS)
  - IOP: 10 mmHg OD, 12 mmHg OS
  - Pupils: 5 → 3 mm in both eyes (OU)
  - Confrontation visual fields: temporal loss OD, central scotoma OS

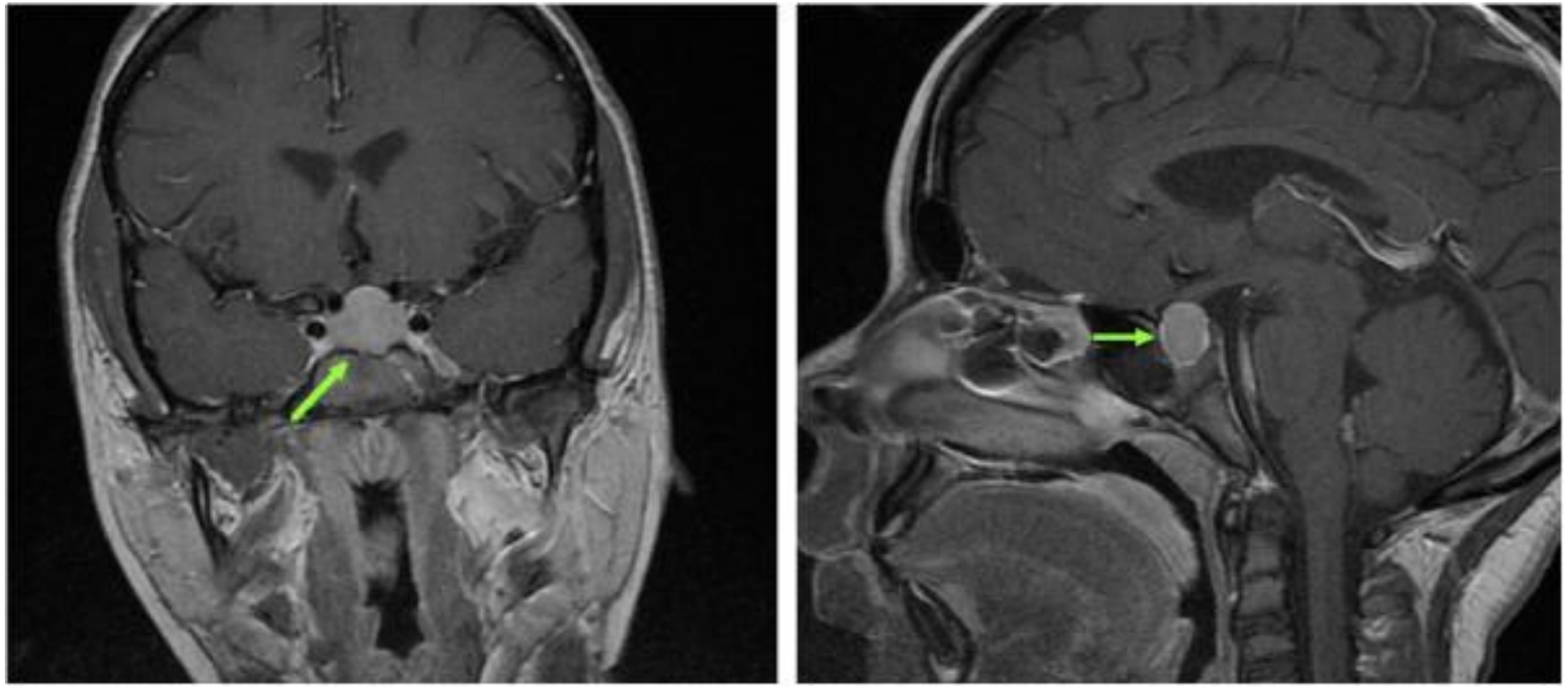
ADVANCES IN Cancer IMMUNOTHERAPY™

Plan

- Imaging?
  - CT/MRI
- Labs?
  - ACTH, TSH, FSH, LH, GH prolactin

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer



ADVANCES IN Cancer IMMUNOTHERAPY™

Treatment

- Steroids
  - Corticosteroids 1 mg/kg/day
  - Dexamethasone 6mg IV Q6hr x 3 days
  - Methylprednisolone 125mg daily
    - Switch to oral prednisone after improvement 1-2 mg/kg qd
- Contact Oncology ASAP

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Summary

- Address the A, B, Cs
- Consider irAEs when patients develop organ dysfunction
- Don’t forget to rule out opportunistic infections and surgical emergencies
- Consider steroids for symptomatic patients, high grade reactions

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Bibliography

- Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Translational Lung Cancer Research*. 2015;4(5):560-575. doi:10.3978/j.issn.2218-6751.2015.06.06.
- Abdel-Wahab N, Shah M, Suarez-Almazor M. Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. *PLOS*. 2016.07.29.
- Jeffrey S. Weber, Katharina C. Kähler, and Axel Hauschild. **Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab.** *Journal of Clinical Oncology* 2012 30:21, 2691-2697
- Horvat T, Adel N, et al. Immune-Related Adverse Events, Need for systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients with Melanoma Treated with Ipilimumab at MSKCC. *Journal of Clinical Oncology* 33, no. 28 (October 2015) 3193-3198.
- Images provided under license by adobe stock