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ADVANCES IN Cancer IMMUNOTHERAPY™

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

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Disclosures

- I have no relevant financial disclosures

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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**

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Timing

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

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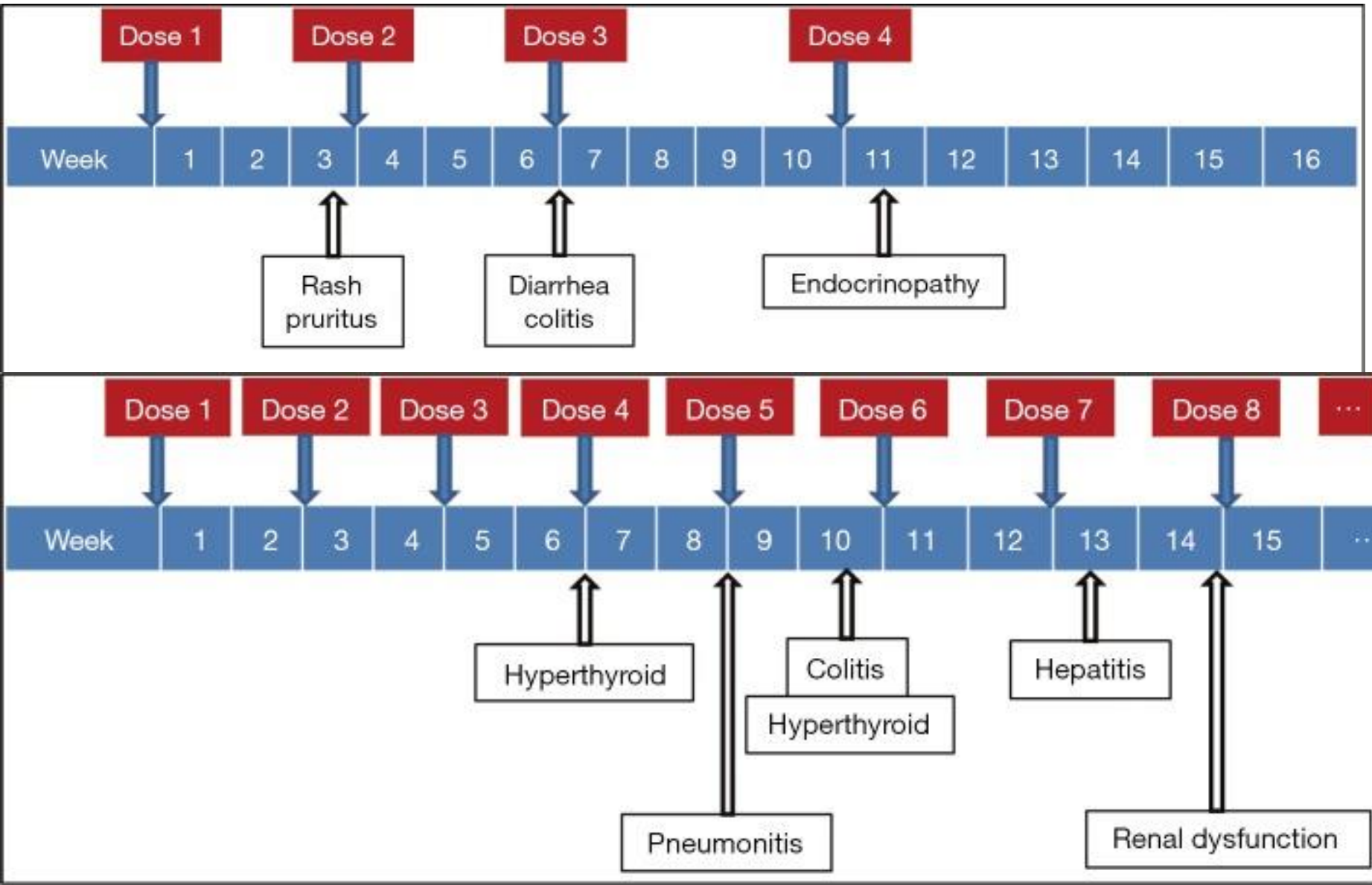

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Dermatologic Toxicity

- Presents three weeks into therapy
- Mild – maculopapular rash with or without symptoms
  - Pruritis, 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)

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Severe

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

Vitiligo

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

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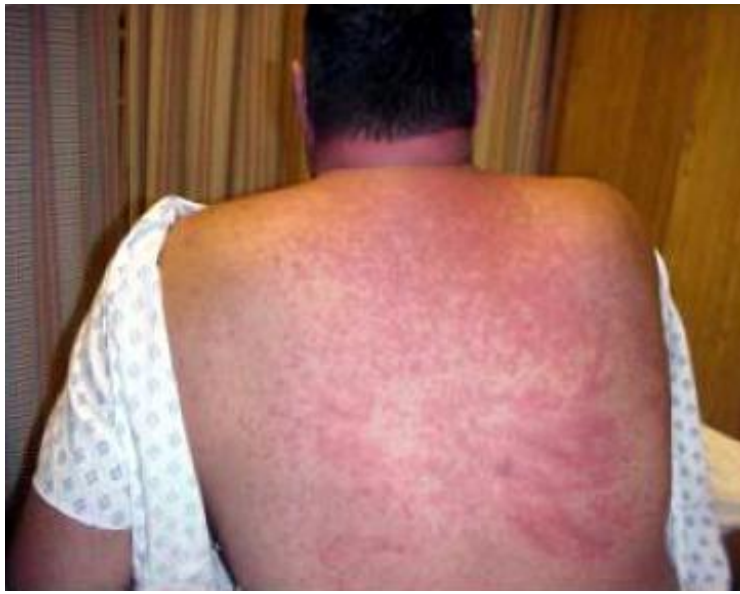
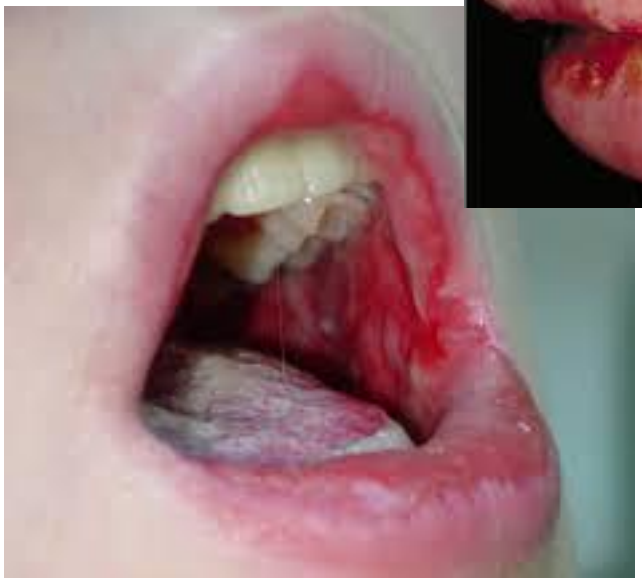
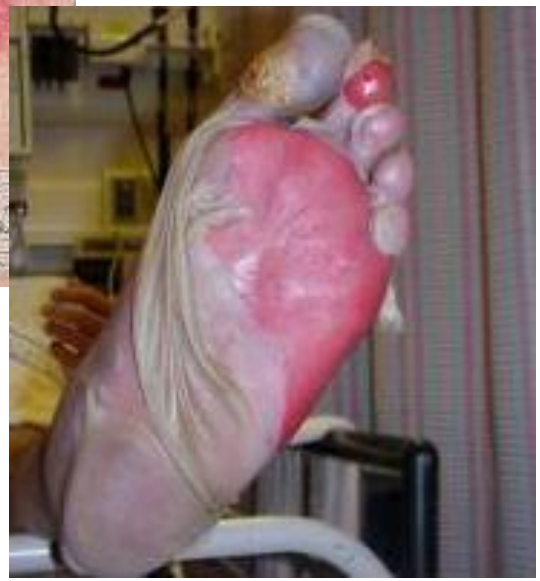
Stevens Johnsons Syndrome (SJS) / TEN (Toxic Epidermal Necrolysis)







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Vitiligo

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Case # 1: 70 yo male with diagnosis of Small Cell lung CA with abdominal pain and diarrhea

Started treatment 6-7 weeks ago

PMH: Small Cell Lung Cancer, HTN, DM

Meds: Nivolumab

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Gastrointestinal i-rAEs

- Diarrhea MC gastrointestinal irAE
- Usually involves distal colon (autoimmune colitis)
- Presents 6 weeks into therapy
- Dose dependent

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- Mild - <4 stools above baseline/day
- Testing
- Treatment
  - Symptomatic: oral hydration & bland diet
  - No corticosteroids
  - Avoid meds
  - Budesonide – no significant difference

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

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Severe

- 7 stools above baseline/day
- Peritoneal signs, ileus or fever
- Admission
- IV hydration
- Rule out perforation
- Stool studies

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- 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
- Consider empiric antibiotics for fever or leukocytosis
- Infliximab 5 mg/kg if no response to corticosteroids
- Consider mycophenolate mofetil for select patients

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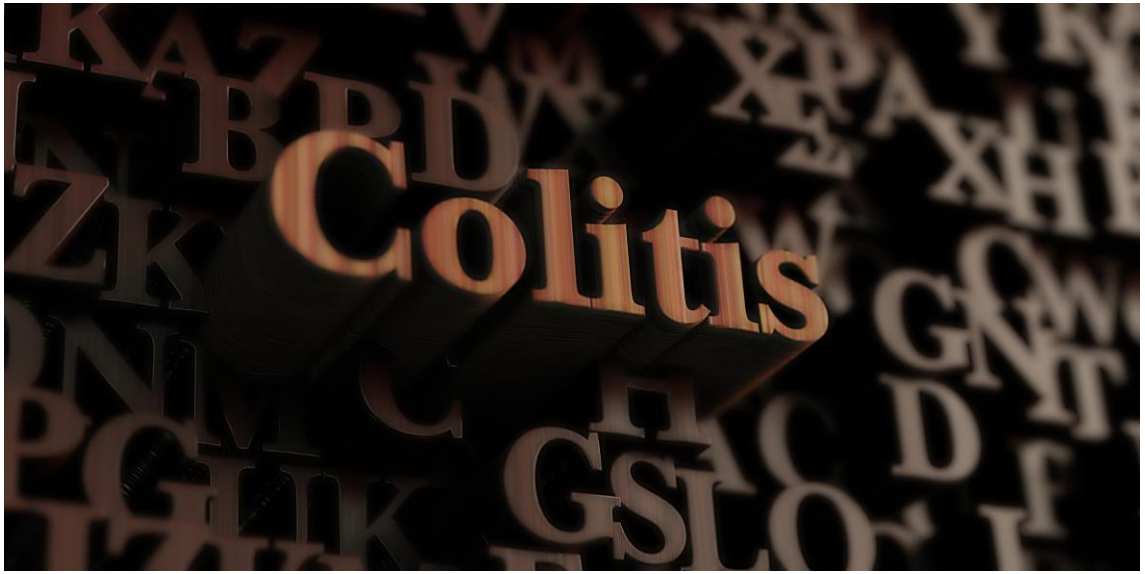
Management

- Fluids & Anagelsia
- Stool Studies
- CT scan
- ABX & steroids



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Case #2 79 yo female with metastatic renal cell CA, DM with several weeks of shortness of breath and intermittent fevers

On arrival SpO2=82% placed on 8L NC

Patient continued to desaturate then placed on HHFNC FiO2= 50% at 40 L/min flow

Has been on a combination of Pembrolizumab/Bevacizumab

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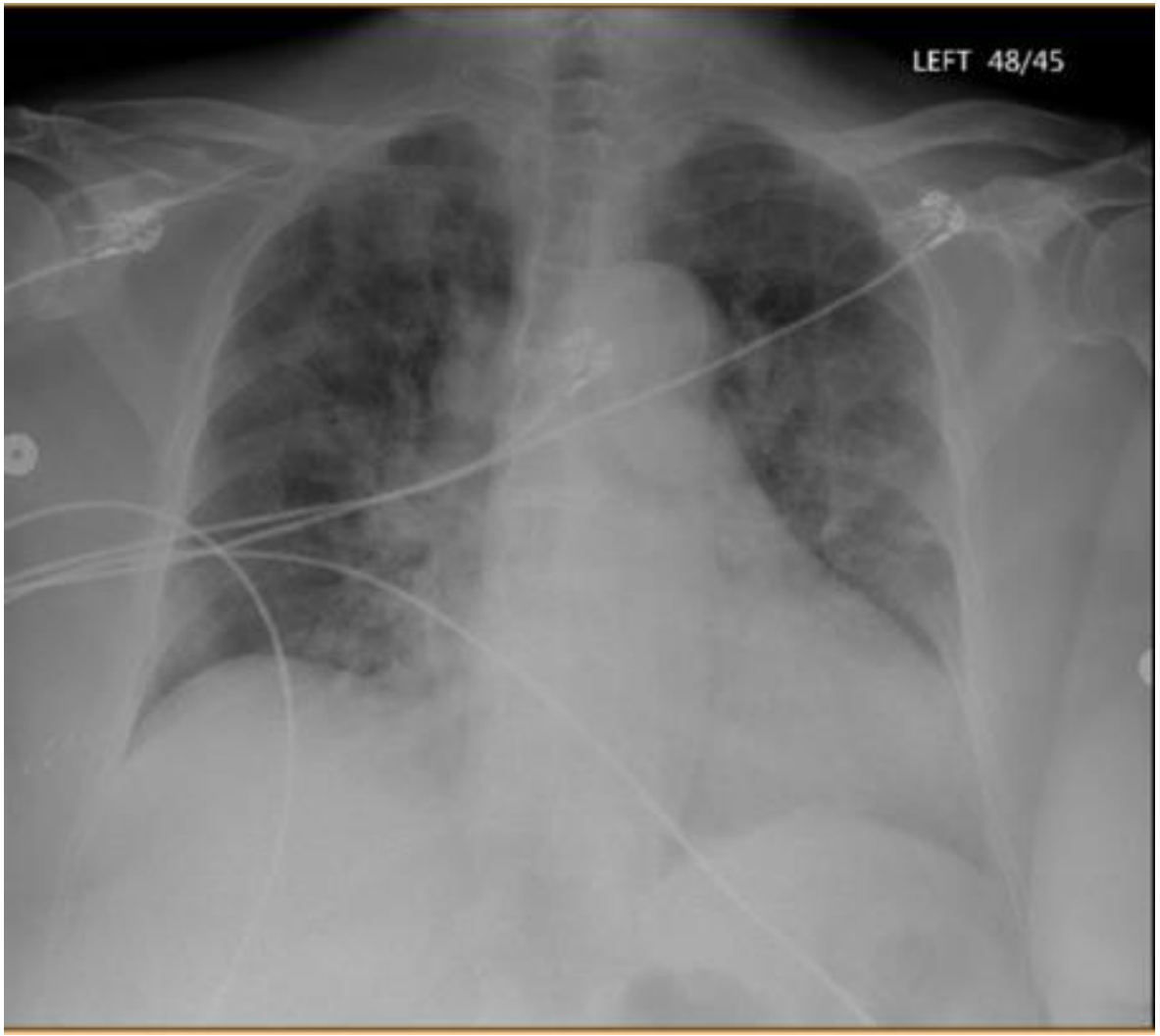
LEFT 48/45

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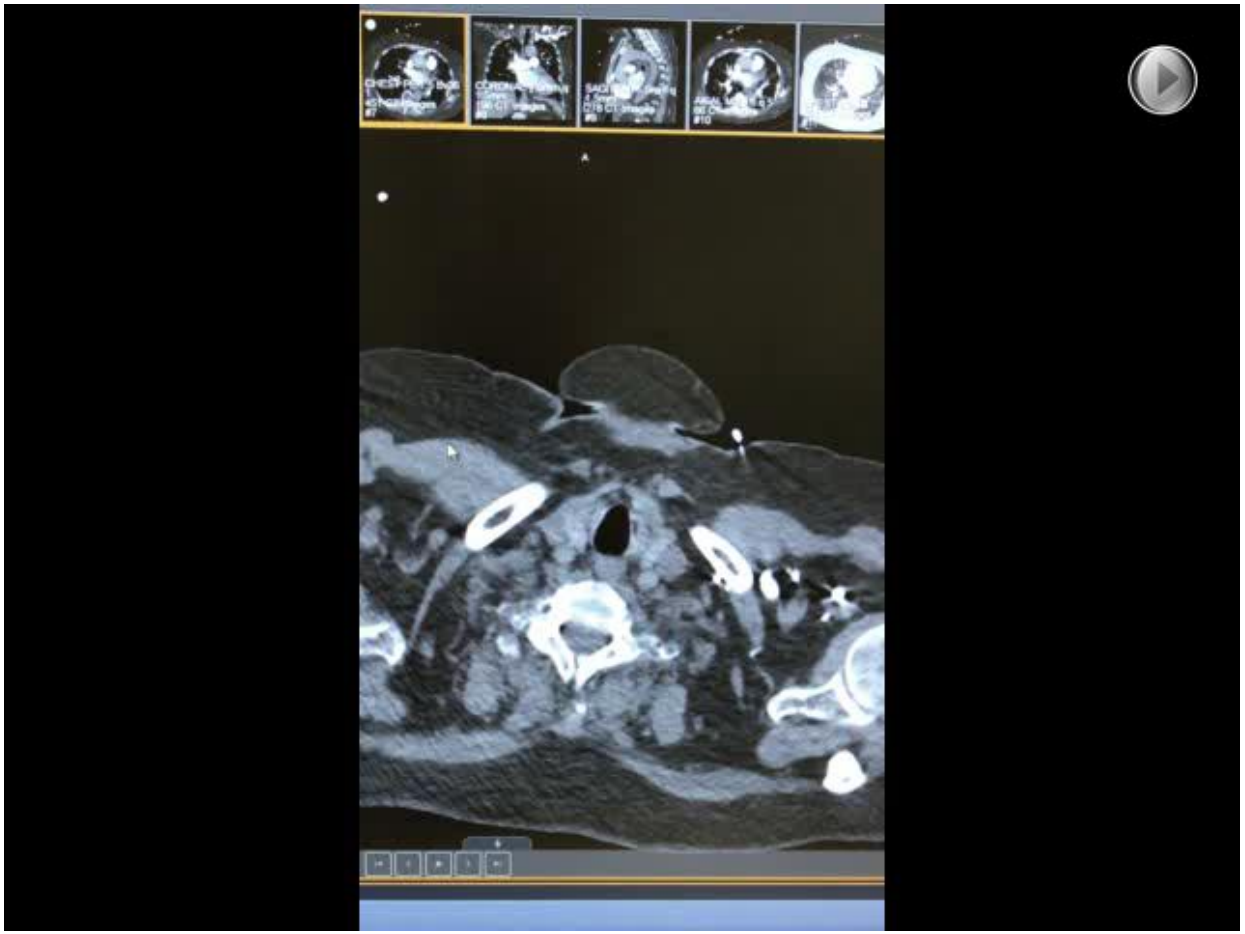

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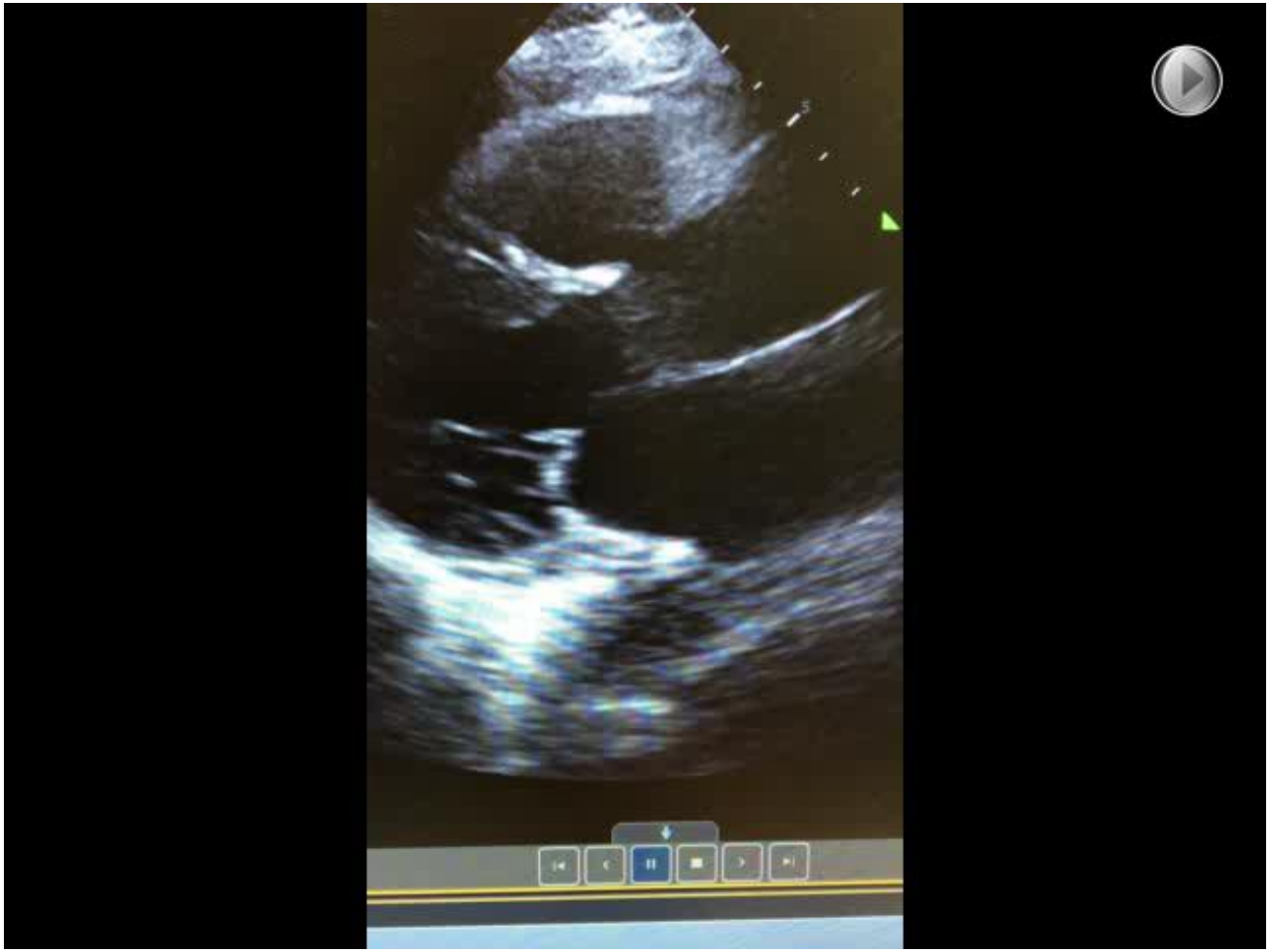

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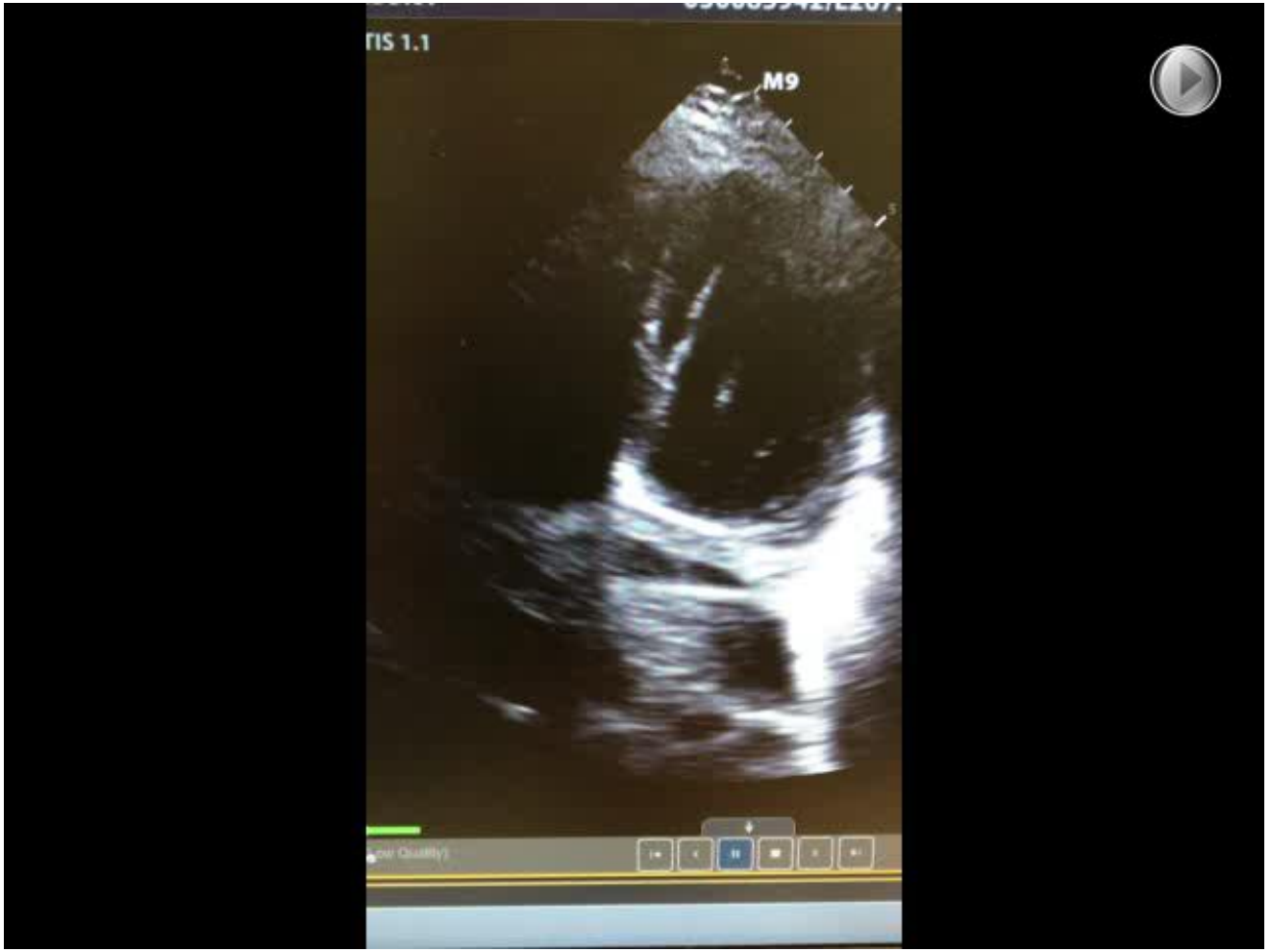

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So what else can cause a similar picture?

- Indolent course
- Non-productive cough in immunocompromised patient
- Reticular interstitial pattern on CXR
- Ground glass opacities on Chest CT

- Pneumocystis jrovecii
- CMV pneumonia
- HSV pneumonia
- RSV
- Idiopathic interstitial pneumonia

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Pneumonitis

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

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Pneumonitis

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

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Hepatotoxity

- 8-12 weeks after therapy initiation

- Avoid ETOH & acetaminophen

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Grade 2 toxicity

- 2.5< AST/ALT <5 times ULN
- 1.5< Bilirubin<3 times ULN
- Corticosteroids 0.5-1 mg/kg/day & 1 mo. taper

Grade ≥3 toxicity

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

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Endocrinopathies

- <10%

- Both CTLA &PD-1 inhibitors

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Hypophysitis

- Fatigue, headaches, visual field defects
- ACTH, TSH, FSH, LH, GH, prolactin
- Imaging – enlarge pituitary gland
- 1-2 months after initiation of therapy
- Corticosteroids 1 mg/kg/day. Or IV dexamethasone 6 mg Q6hr x 3 days, or methylprednisolone 125 mg daily

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Endocrinopathies cont.

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

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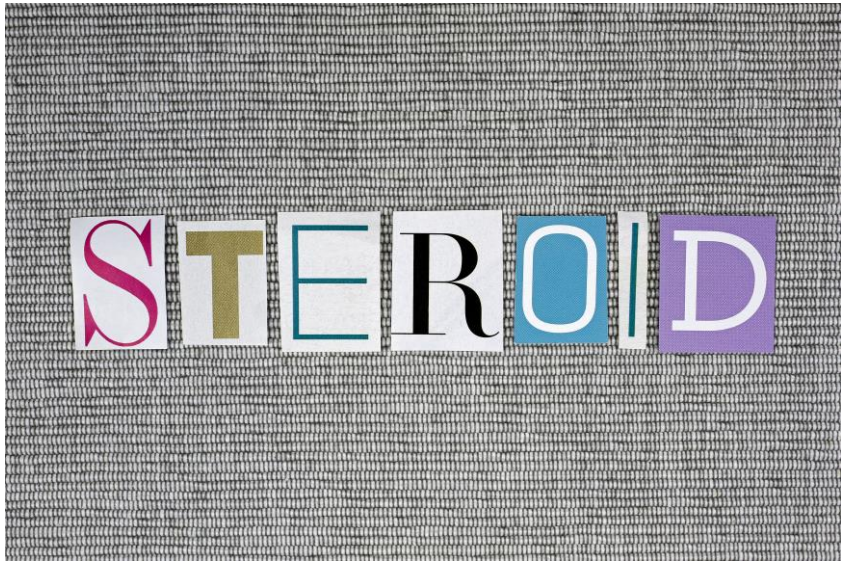
Common Medications

- Corticosteroids
  - **Prednisone**
  - Dexamethasone
  - Methylprednisolone
  - Hydrocortisone
  - Cortisone
- Mycophenolate mofetil (CellCept)
  - Standard BID
- TNF inhibitors
  - Infliximab
  - Adalimumab
  - Others



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Pancreatic

- Elevation amylase & lipase
  - With both CTLA-4 &PD1 inhibitors
  - Without overt pancreatitis– monitor
  - Grade 3-4 with symptoms – hold therapy

- New onset diabetes with DKA
  - Normal ED treatment
  - Aggressive treatment of DKA

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Other adverse effects

Source: SlideShare.net: Hydration is Key by HDX Hydration Mix

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Renal Insufficiency

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

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Ophthalmologic

- <1%
- Episcleritis
- Uveitis
- Conjunctivitis
- Topical corticosteroids – prednisolone acetate 1%

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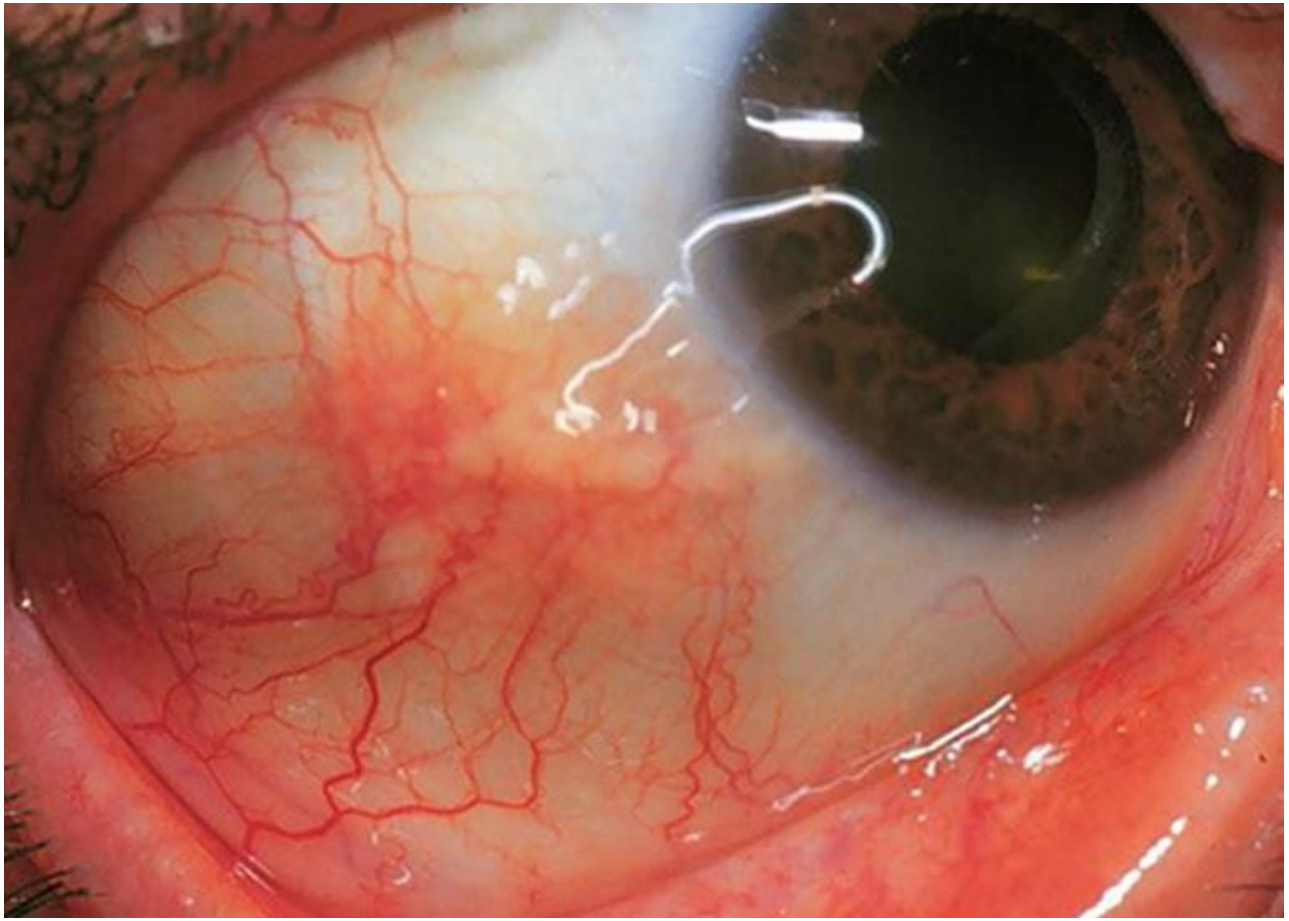

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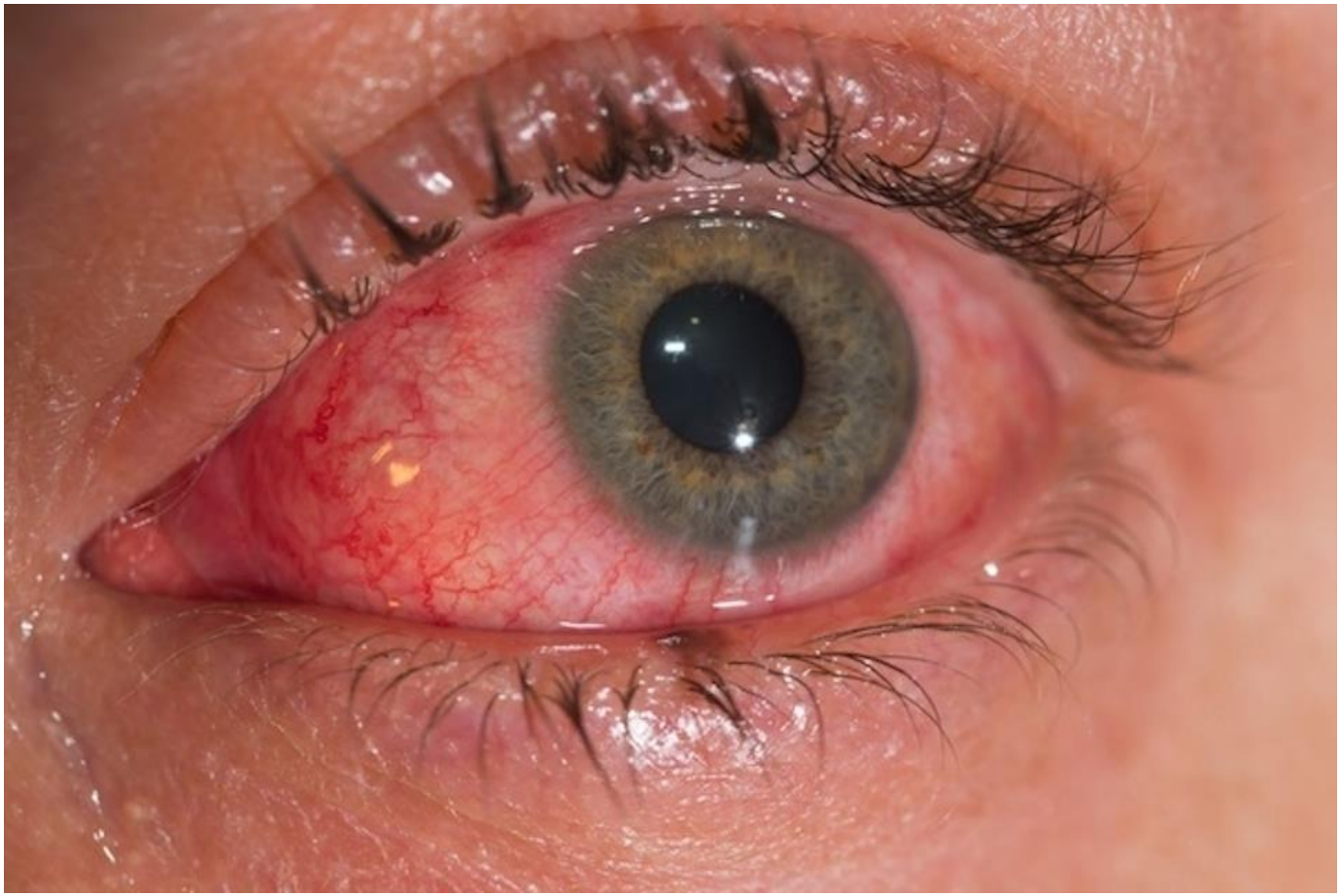

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Rare irAEs

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

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Case #3: 54-year-old male with NSCLC

- New immunotherapy 8 weeks ago for lung cancer
- Vision is blurry, & glasses don't work anymore
  - Denies eye pain
  - Mild HA "because he reads a lot & his glasses don't work anymore"
- Exam
  - VA w/o correction: 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

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Plan

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

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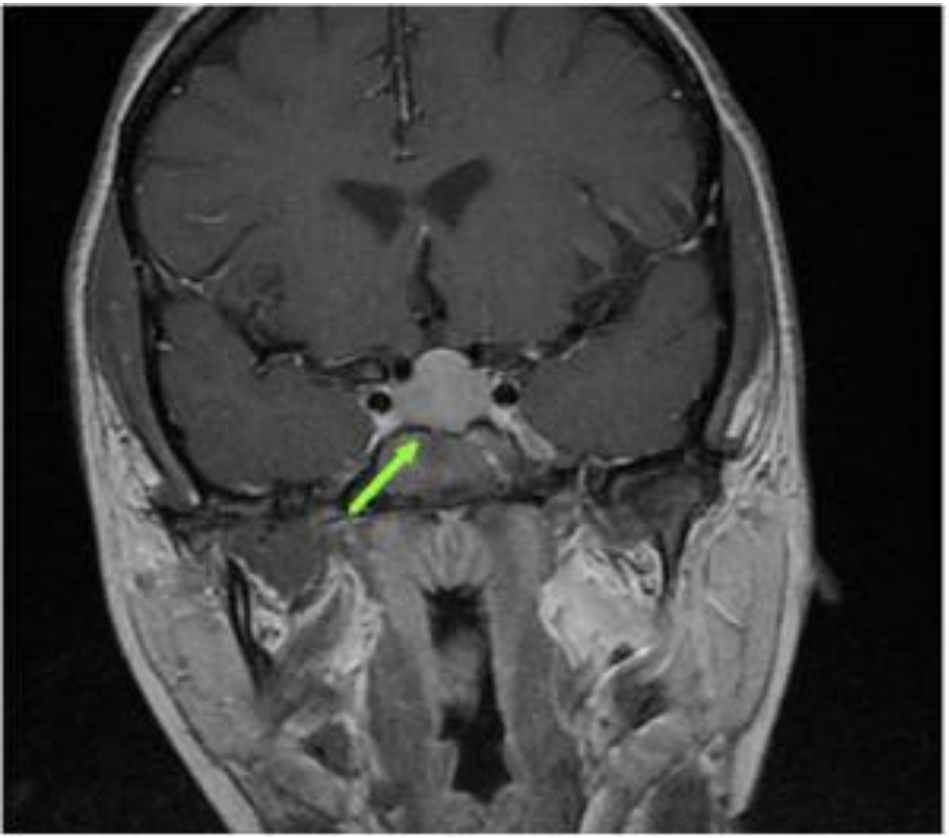

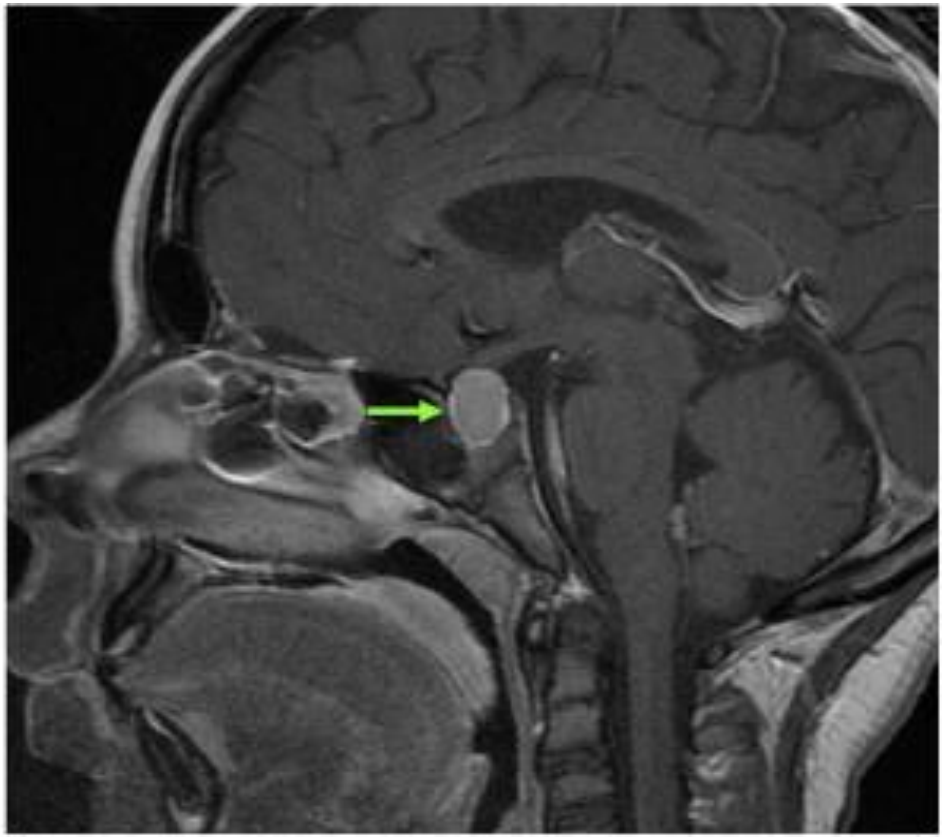

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Treatment

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

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Summary

- Address instability first : A,B,Cs
- Consider irAEs when patient undergoing develop organ specific dysfunction
- Don’t forget to rule out Opportunistic infections
- Just like in Rheumatologic and Immune disorders Steroids should be initiated when Grade 3 or 4 AEs encountered

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The End

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