ADVANCES IN Cancer IMMUNOTHERAPY™

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

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

None

I will be discussing non-FDA approved treatments during this presentation

No treatments currently FDA approved for irAEs (immune-related adverse events)

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Matterhorn / Monte Cervino

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Mechanism

- CTLA-4 and PD-1
  - Involved in maintaining appropriate immune response
  - Down regulation and prevention of inappropriate activity against self-antigens.
  - Activity/targets normal tissues
  - 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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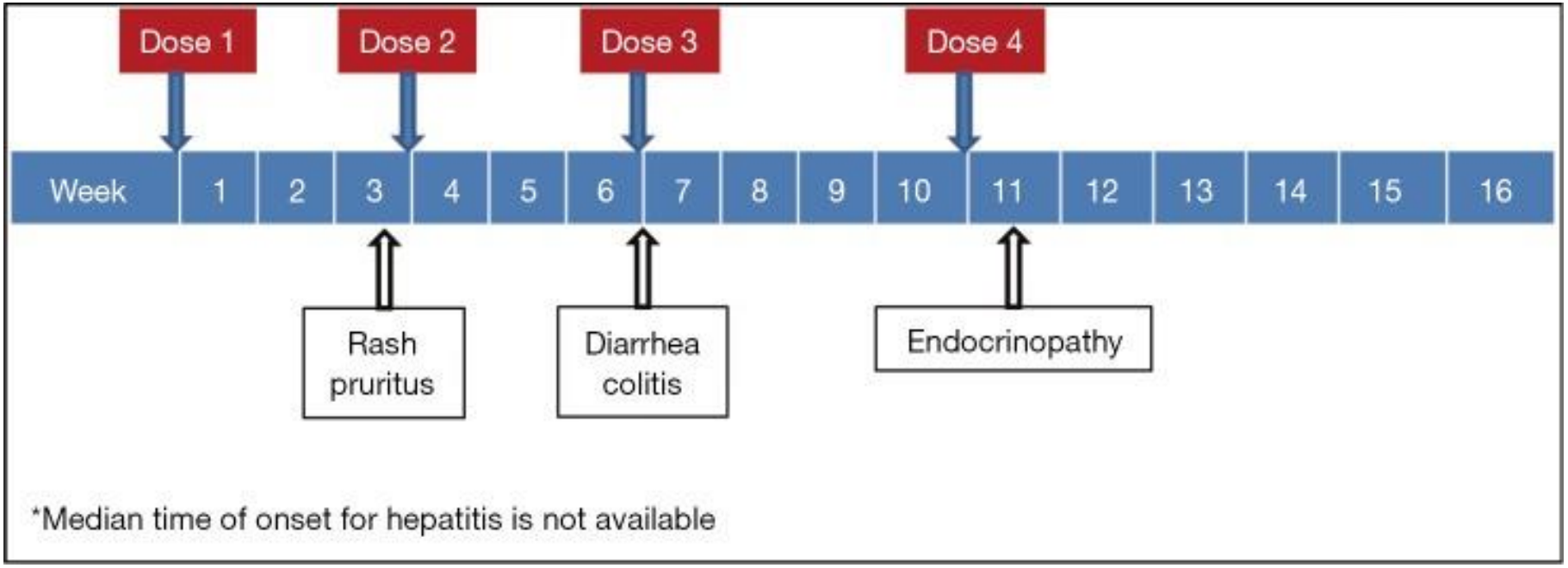

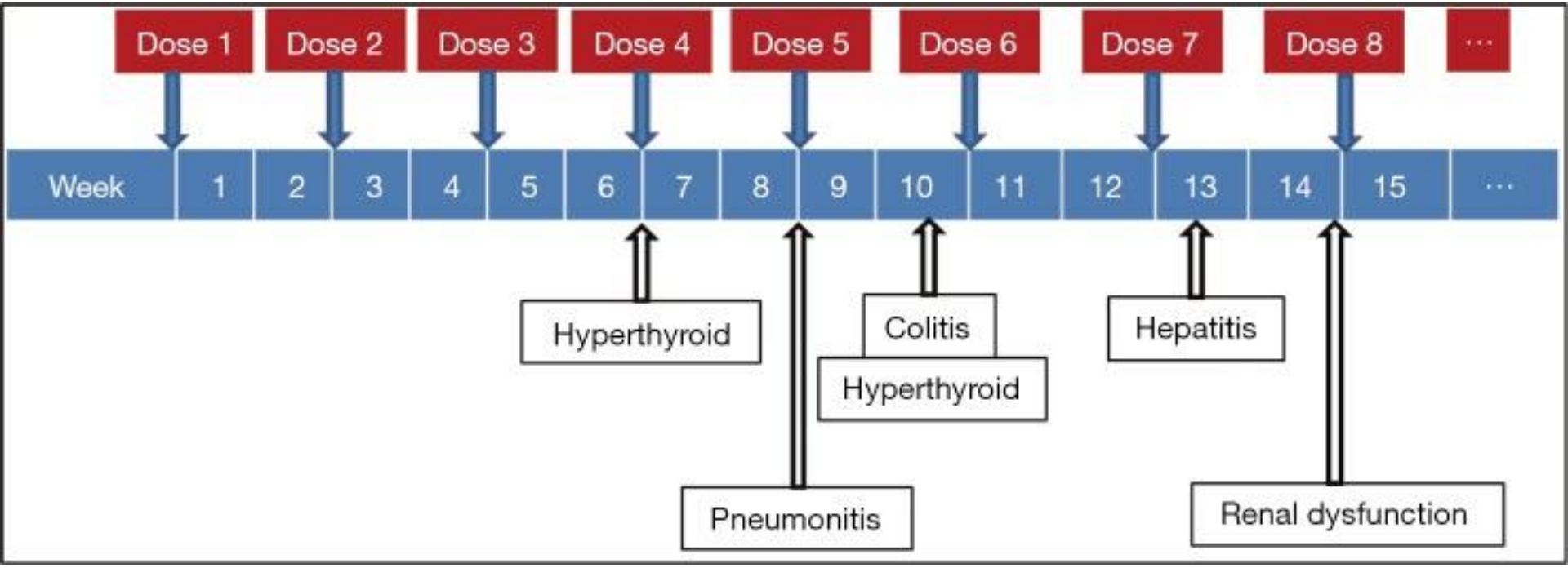

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Common Medications

- Corticosteroids
  - **Prednisone 10mg**
  - Dexamethasone 1.5mg
  - Methylprednisolone 8mg
  - Hydrocortisone 40mg
  - Cortisone 50mg
- Mycophenolate mofetil (CellCept)
  - Standard 500mg BID
- TNF inhibitors
  - Infliximab (Remicade)
  - Adalimumab (Humira)
  - Others

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Dermatologic Toxicity

- Presents 3 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 1 week (0.5-1mg/kg/day)

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Dermatologic Toxicity cont.

- Severe
  - Shows signs of blister, dermal ulceration, necrotic, bullous or hemorrhagic.
  - Systemic corticosteroids 1-2 mg/kg/day prednisone equiv.
  - Taper over one month following improvement.
- Vitiligo
  - Most cases permanent
  - No treatment
  - Intra oral lesions-consider candidiasis.

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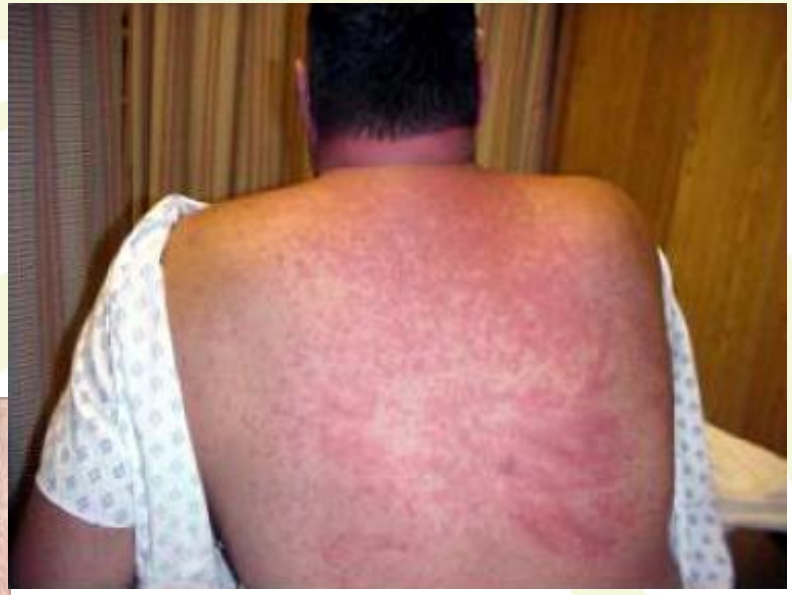

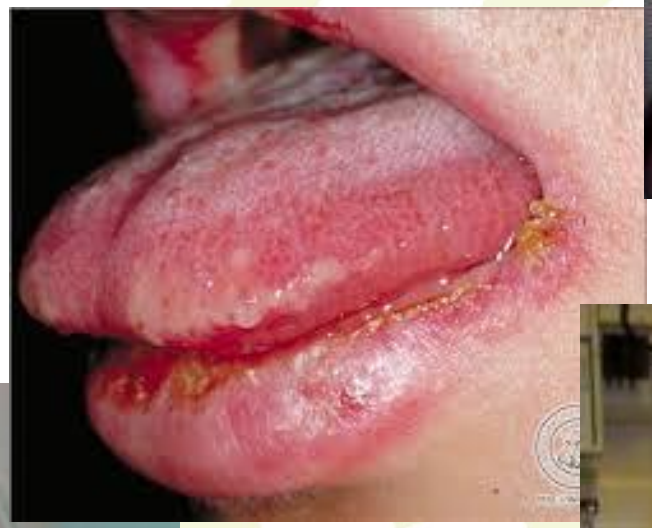

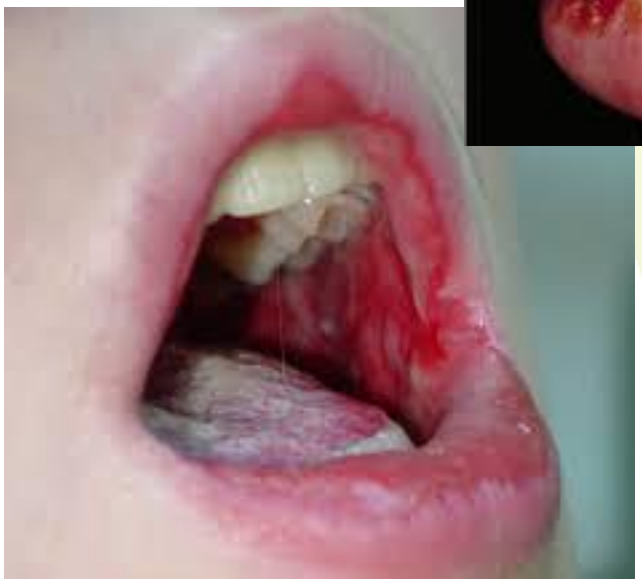

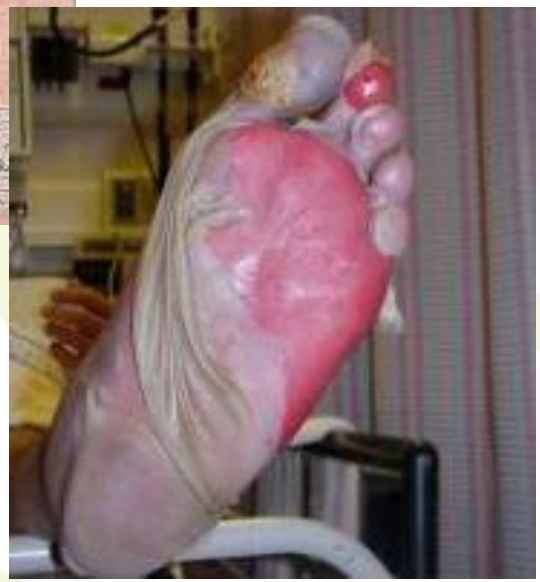

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Vitiligo

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Diarrhea / Colitis

- Presents 6 weeks into therapy
- Dose dependent
- Mild - <4 stools above baseline/day
  - Testing - C. diff., lactoferrin, O & P, stool culture
  - Symptomatic tx – oral hydration, bland diet
  - No corticosteroids
  - Avoid loperamide, diphenoxylate/atropine – mask more severe symptoms
  - Budesonide-no sig difference

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Diarrhea / Colitis cont.

- Moderate – 4-6 stools above daily baseline, Abd pain, blood or mucus in stool.
  - Testing - C. diff., lactoferrin, O & P, stool culture
  - Systemic corticosteroids 0.5/mg/kg/day equiv. if symp >1 week

Diarrhea / Colitis cont.

- Severe - >7 stools above baseline per day, peritoneal signs, ileus or fever.
  - Admission
  - IV hydration
  - Rule out perforation
  - Stools studies

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Diarrhea / Colitis cont

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

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Hepatotoxity

- 8-12 weeks after therapy initiation
- Avoid ETOH and acetaminophen
- Grade 2 toxicity
  - AST or ALT >2.5 but <5 times ULN
  - Bilirubin >1.5 but <3 times ULN
  - Corticosteroids 0.5-1mg/kg/day
    - Tape over 1 month after improvement
- Grade ≥3 toxicity
  - Admission
  - Methylprednisolone IV 125mg/day
  - Consider mycophenolate mofetil 500mg PO Q12hrs
    - If no improvement in 3-5 days of corticosteroid tx.

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Endocrinopathies

- <10%
- Both CTLA and PD-1 inhibitors
- Hypophysitis
  - Fatigue, headaches, visual field defects
  - ACTH, TSH, FSH, LH, GH, prolactin.
  - Imaging – enlarge pituitary gland
  - 1-2 months after initiation of therapy
  - Corticosteroids 1mg/kg/day. Or IV dexamethasone 6mg Q6hr x 3 days, or methylprednisolone 125mg daily.
    - Switch to oral prednisone after improvement 1-2mg/kg daily

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Endocrinopathies cont.

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

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Pneumonitis

- Occur with CTLA-4 and PD1 inhibitors
- 5 months after treatment initiation
- New cough or dyspnea
- Grade 2
  - Admission
  - Methylprednisolone 1mg/kg/day
    - Taper over 1 month after improvement seen
- Grade 3-4
  - Admission
  - Methylprednisolone 2-4mg/kg/day
    - Taper over 6 weeks after improvement seen

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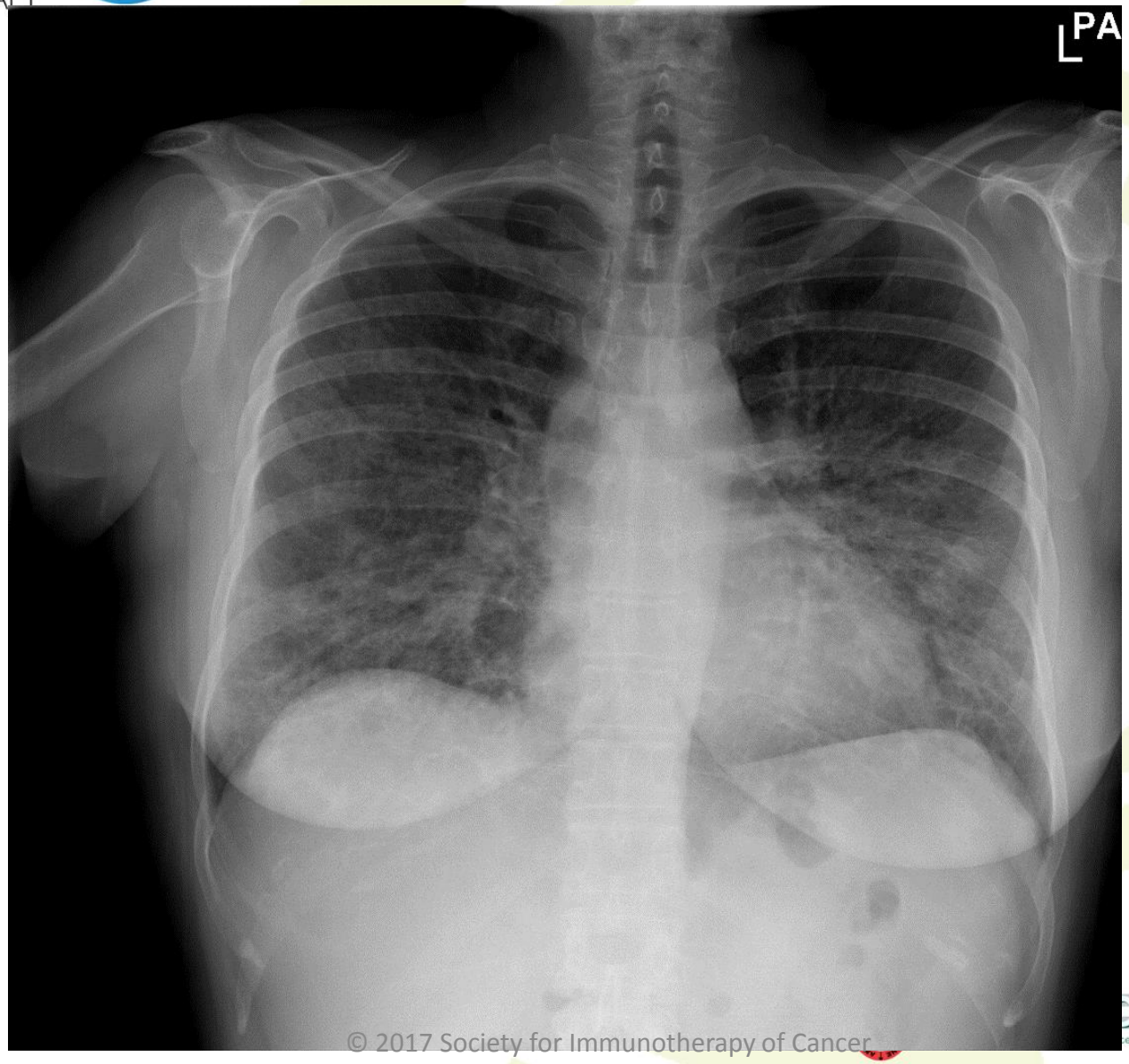

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Pancreatic

- Elevation amylase and lipase
  - With both CTLA-4 and 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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Renal Insufficiency

- <1%
- Grade 1: up to 1.5 times above baseline
  - Monitor weekly
- Grade 2 to 3: 1.5-6 times baseline
  - Monitor every 24-48 hours
  - Prednisolone 0.5-1mg/kg
- 10-12 months after initiation of treatment
- Full recovery with high dose corticosteroids. (>40mg/day)

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Ophthalmologic

- Episcleritis
- Uveitis
- Conjunctivitis
- <1%
- Topical corticosteroids-Prednisolone acetate 1%

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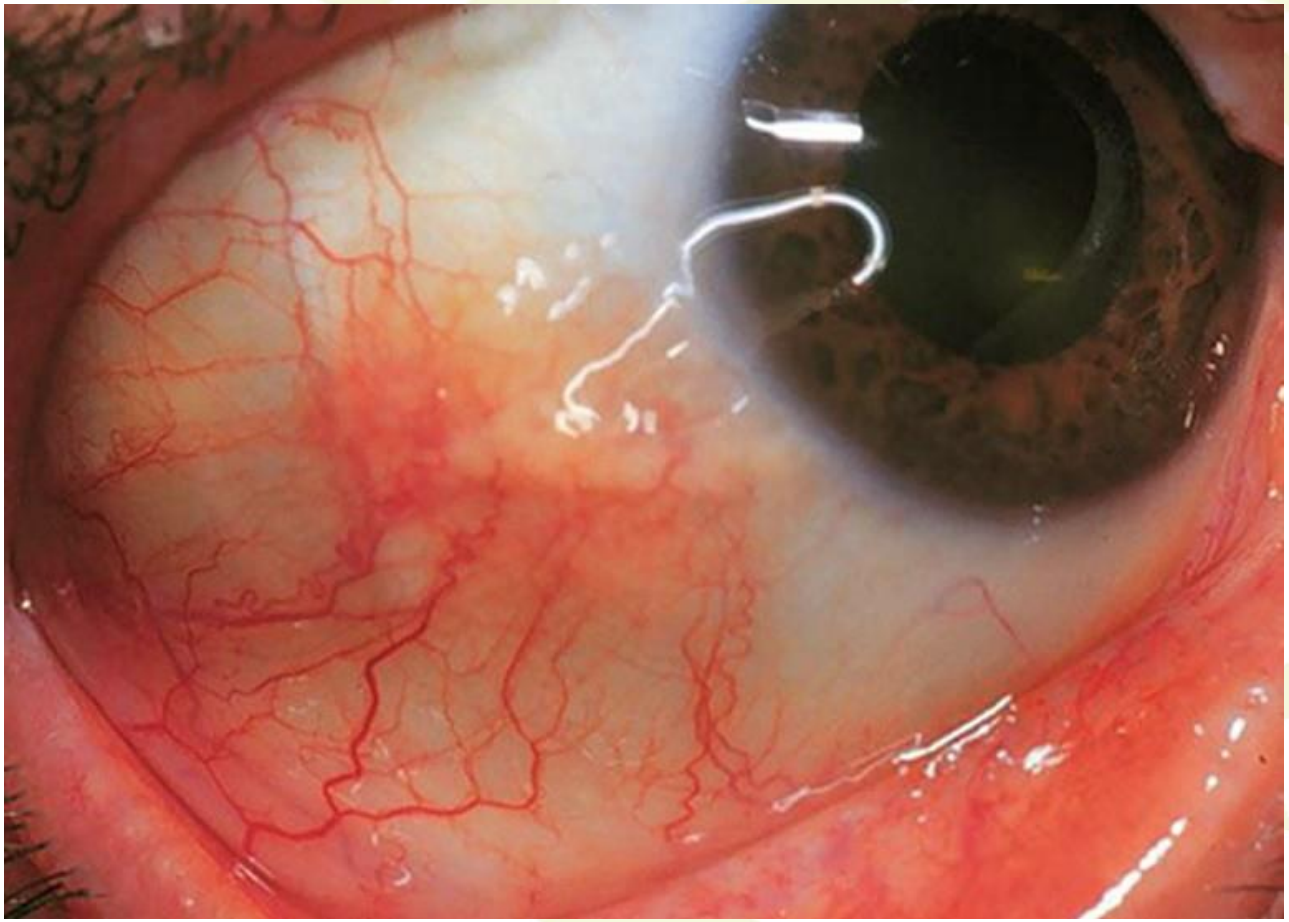

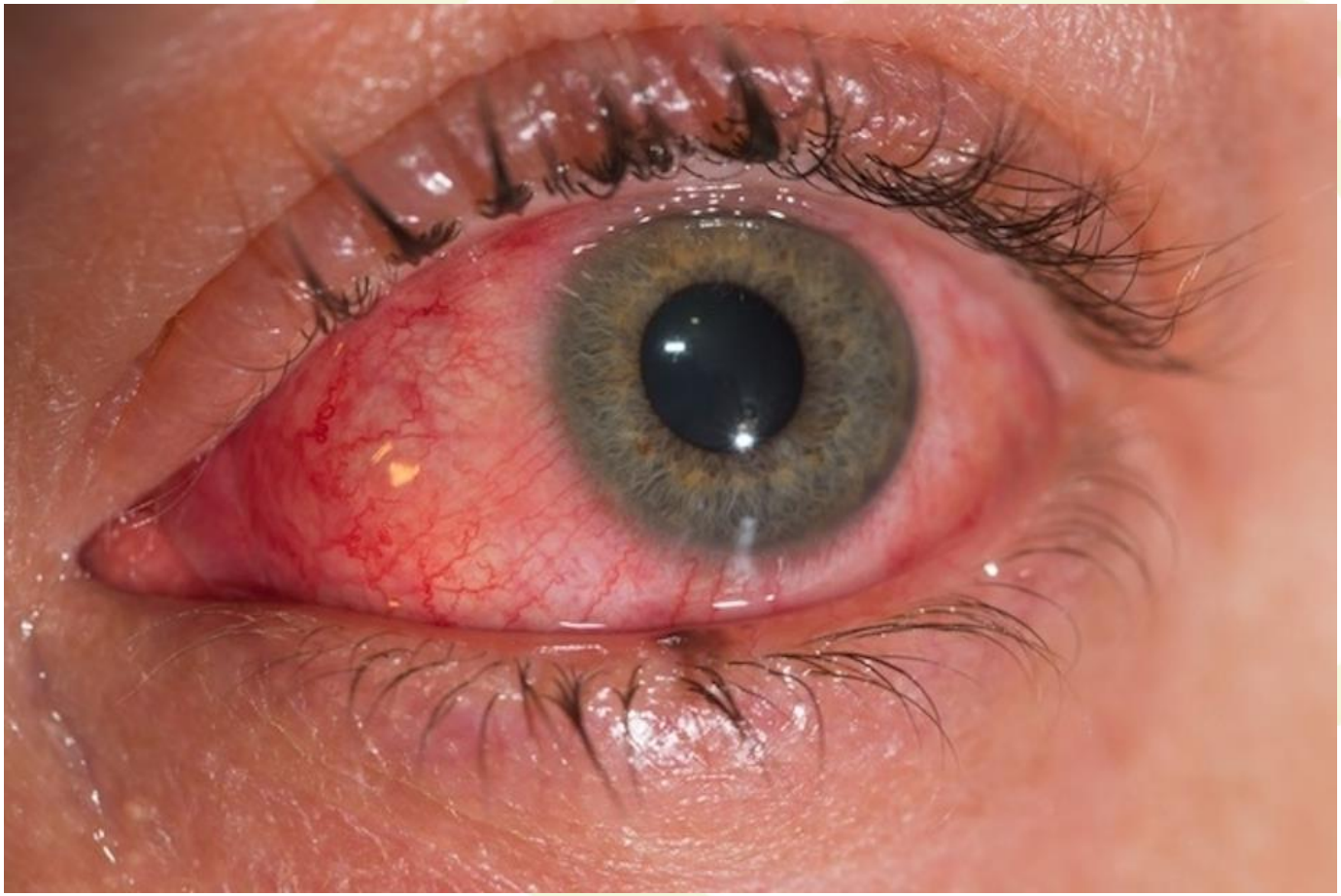

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Rare irAEs

- <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 #1: 67yo female with Melanoma

- New “Chemotherapy” initiated 4 weeks ago. Immunotherapy, ipilmumab
- >8 stools with mucus.
- Feeling weak and lightheaded when she stands.
- States she feels hot but doesn't have a thermometer.
- Told to go to ED.

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ED Report

- Exam
  - Vitals P:102, BP: 112/65 +Orthostatic, T: 98.9, 98%
  - Belly: mild tender, no guarding or rebound. Hypoactive BS

- Plan
  - IV hydration
  - Blood Work
  - Stool studies (C. diff., lactoferrin, O & P, stool culture)

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Results

- Stool
  - Neg
- Blood work
  - Neg
- Pt feeling better after 1L crystalloid. Diarrhea continues same.

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Treatment

- Consider empiric antibiotics for fever or leukocytosis
- Admission
- Systemic corticosteroids 1-2mg/kg/day equiv, if no perforation.
  - Hold if clinically stable until stool studies available (24hrs)
- Contact Hem/Onc ASAP

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Case #2: 54yo male with NSCLC

- Initiated new immunotherapy 8 weeks ago for lung cancer
- He says vision is blurry, his glasses don't work anymore. He thinks he needs a new pair.
  - Denies eye pain.
  - Mild HA "because he reads a lot and his glasses don't work anymore
- Exam
  - Visual acuity without correction: 20/25 right eye (OD), 20/125 left eye (OS)
  - Intraocular pressure: 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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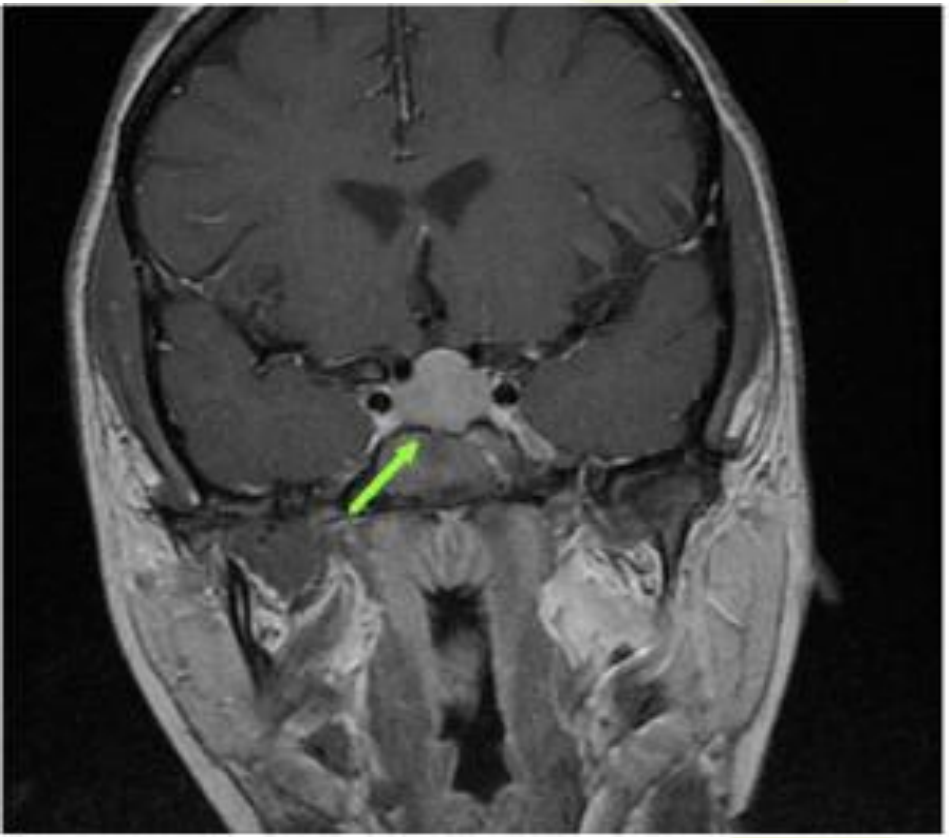

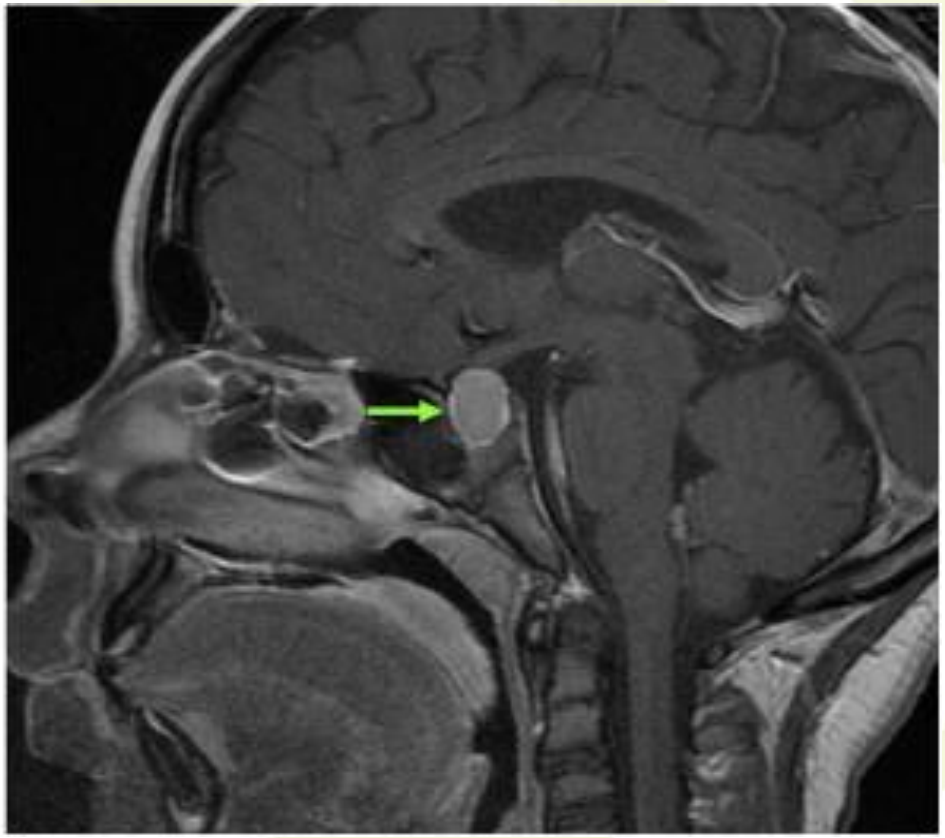

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Treatment

- Corticosteroids 1mg/kg/day. Or IV dexamethasone 6mg Q6hr x 3 days, or methylprednisolone 125mg daily.
  - Switch to oral prednisone after improvement 1-2mg/kg daily
- Contact Hem/Onc ASAP

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Questions??

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