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

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American Academy of Emergency Medicine

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Disclosures

- No relevant financial relationships to disclose

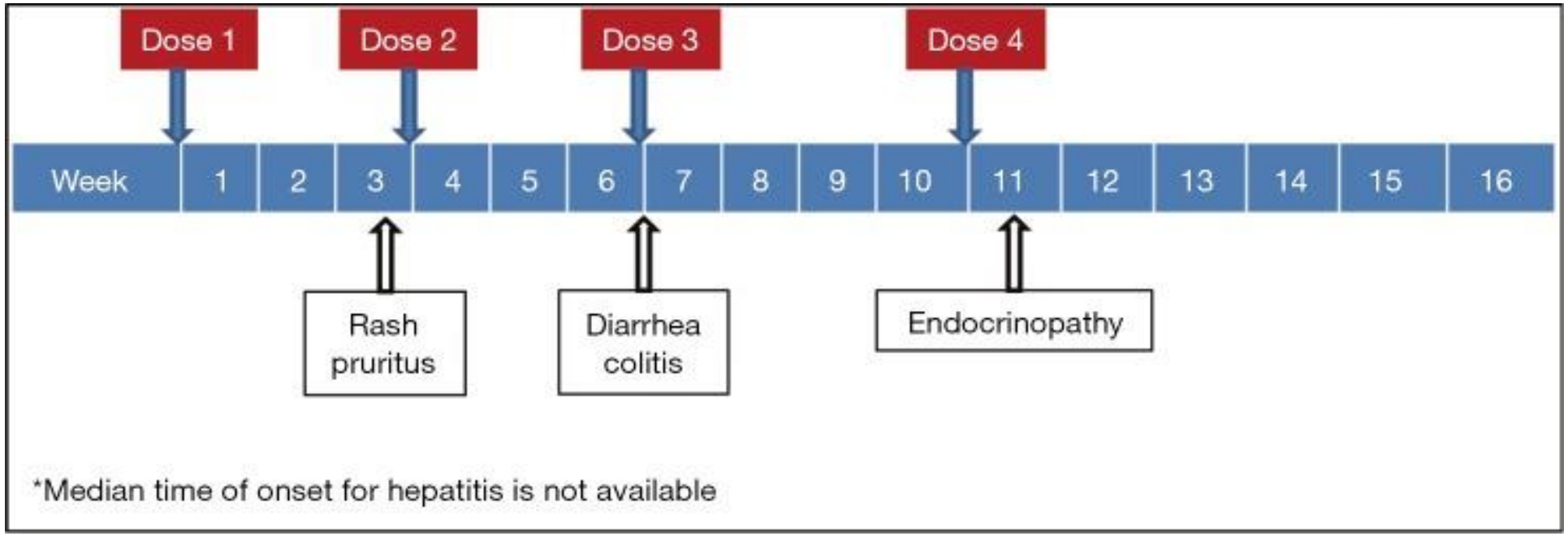
CTLA-4 and PD-1/PD-L1
Immune checkpoint mechanisms

- Involved in maintaining appropriate immune response
- Downregulates & prevents inappropriate activity
- Autoimmune type response
- Thinking “Chemo” will lead to incorrect AE strategy
- **Immunotherapy AEs similar to Graft versus Host disease**

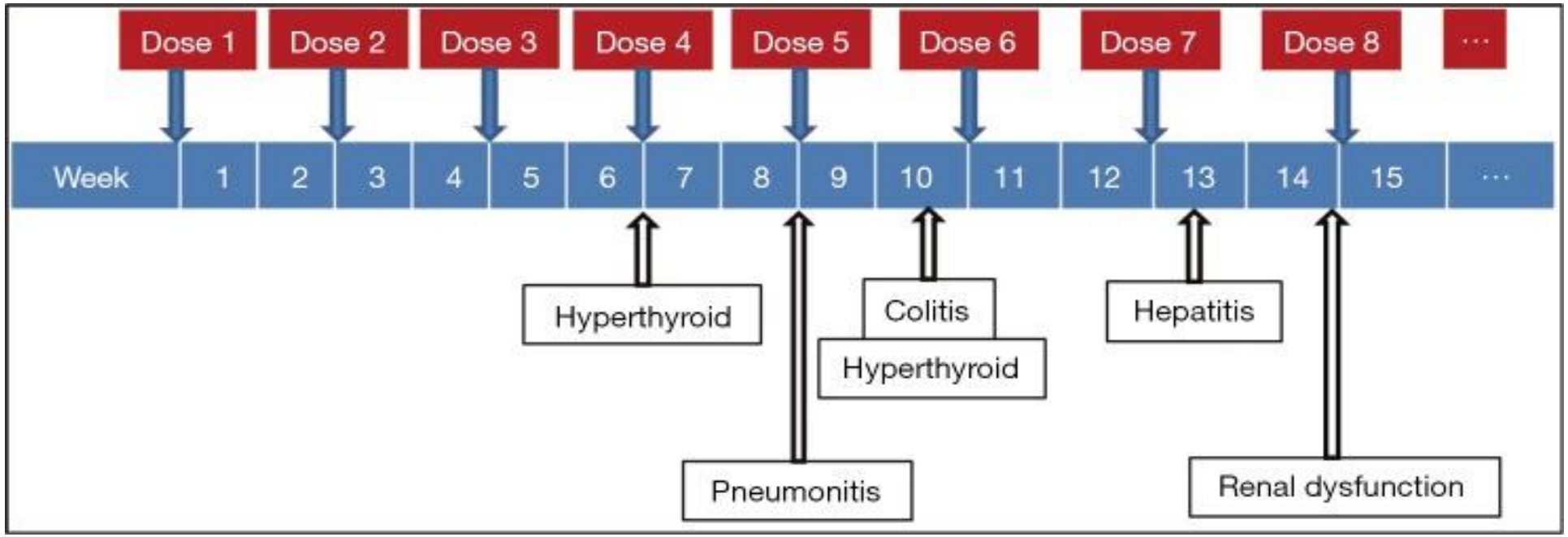
Timing of irAE incidence

- Most irAEs occur within three months of treatment initiation
- irAEs can occur past treatment completion
- Some irAEs are dose-dependent
- ~10% of overall irAEs grade 3/4

Timing of irAE incidence



Timing of irAE incidence



Common medications for irAE treatment

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

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Dermatologic Toxicity

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Dermatologic toxicity presentation

- Often presents ~ three weeks post-therapy initiation
- Mild – maculopapular rash with or without symptoms
  - Pruitis, burning, tightness
  - 10% - 30% TBSA
  - Limiting ADL's
  - Topical steroids, hydroxyzine, diphenhydramine
  - Cort
- Moderate – diffuse, nonlocalizing rash
  - 30% - 50% TBSA
  - Topical corticosteroids, hydroxyzine, diphenhydramine
  - Consider systemic corticosteroids if no improvement within one week (0.5 – 1mg/kg/day)

Dermatologic toxicity presentation

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

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

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

Vitiligo

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Diarrhea/ Colitis

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Diarrhea/ colitis presentation

- Mild - <4 stools above baseline/day

- Treatment
  - Symptomatic: oral hydration & bland diet
  - No corticosteroids
  - Avoid medications
  - Budesonide – no significant difference

Diarrhea/ colitis presentation

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

Diarrhea/ colitis presentation

- Severe – >6 stools above daily baseline
  - Peritoneal signs, ileus or fever
  - Admission
  - IV hydration
  - Rule out perforation
  - Stool studies

Diarrhea/ colitis presentation

- Severe – >6 stools above daily baseline
  - 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 non responsive to corticosteroids
  - Consider mycophenolate mofetil for select patients

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Hepatotoxicity

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Hepatotoxicity presentation

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

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Endocrinopathies

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Endocrinopathy presentation

- >10% all reported irAE cases
- Can arise while receiving checkpoint inhibitors
- Hypophysitis
  - 1-2 months after initiation of therapy
  - Fatigue, headaches, visual field defects
  - ACTH, TSH, FSH, LH, GH, prolactin
  - Imaging – enlarged pituitary gland
  - Corticosteroids 1 mg/kg/day, or IV dexamethasone 6 mg Q6hr x 3 days, or methylprednisolone 125 mg daily

Endocrinopathy presentation

- 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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Pneumonitis

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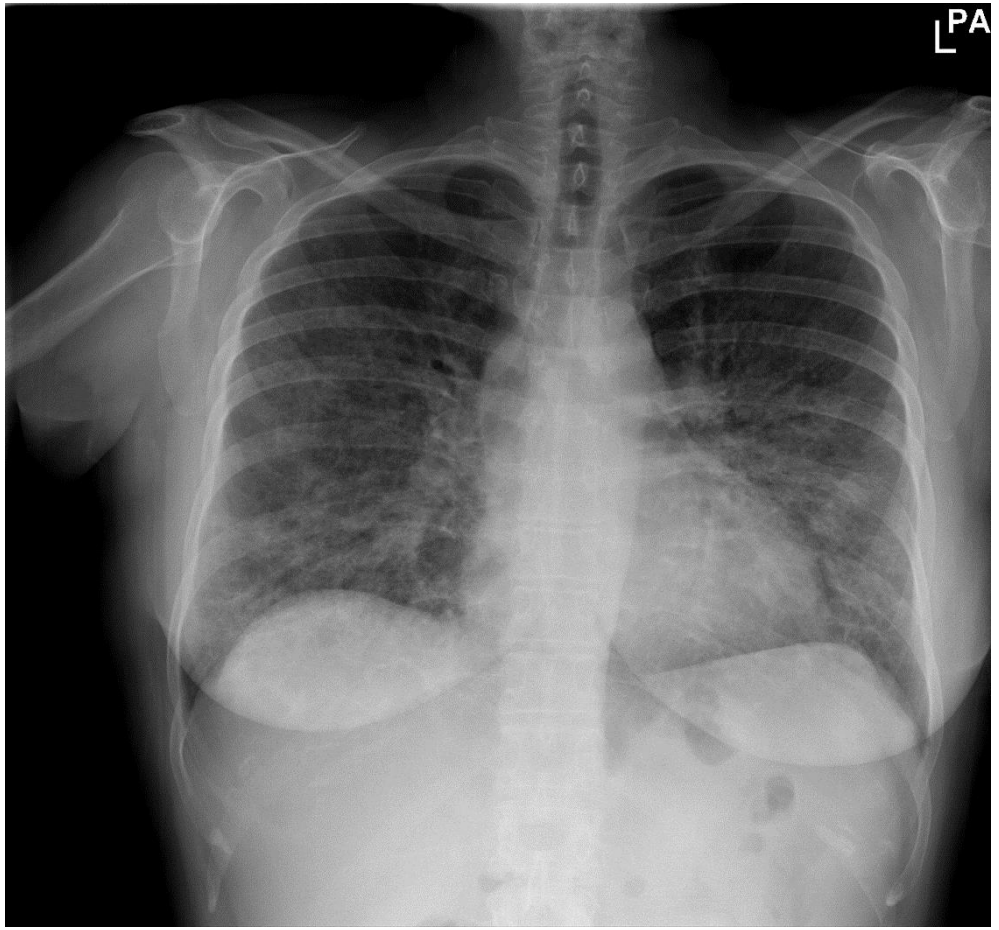
Pneumonitis presentation

- Can arise during treatment with checkpoint inhibitors
- Symptomatic ~ 5 months after treatment initiation
- New cough or dyspnea
- Multiple grades
  - Grade 2
    - Admission
    - Prednisone/prednisolone
      - Taper over one month after improvement seen
  - Grade 3-4
    - Admission
    - Prednisone/prednisolone
      - Taper over six weeks

Pneumonitis presentation



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Pancreatic irAEs

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Pancreatic irAE presentation

- Elevated amylase and/or lipase
  - Can arise during treatment with checkpoint inhibitors
  - Without overt pancreatitis – monitor patient
  - Symptomatic Grade 3/4 incidences – hold therapy

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

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Renal insufficiency

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Renal insufficiency presentation

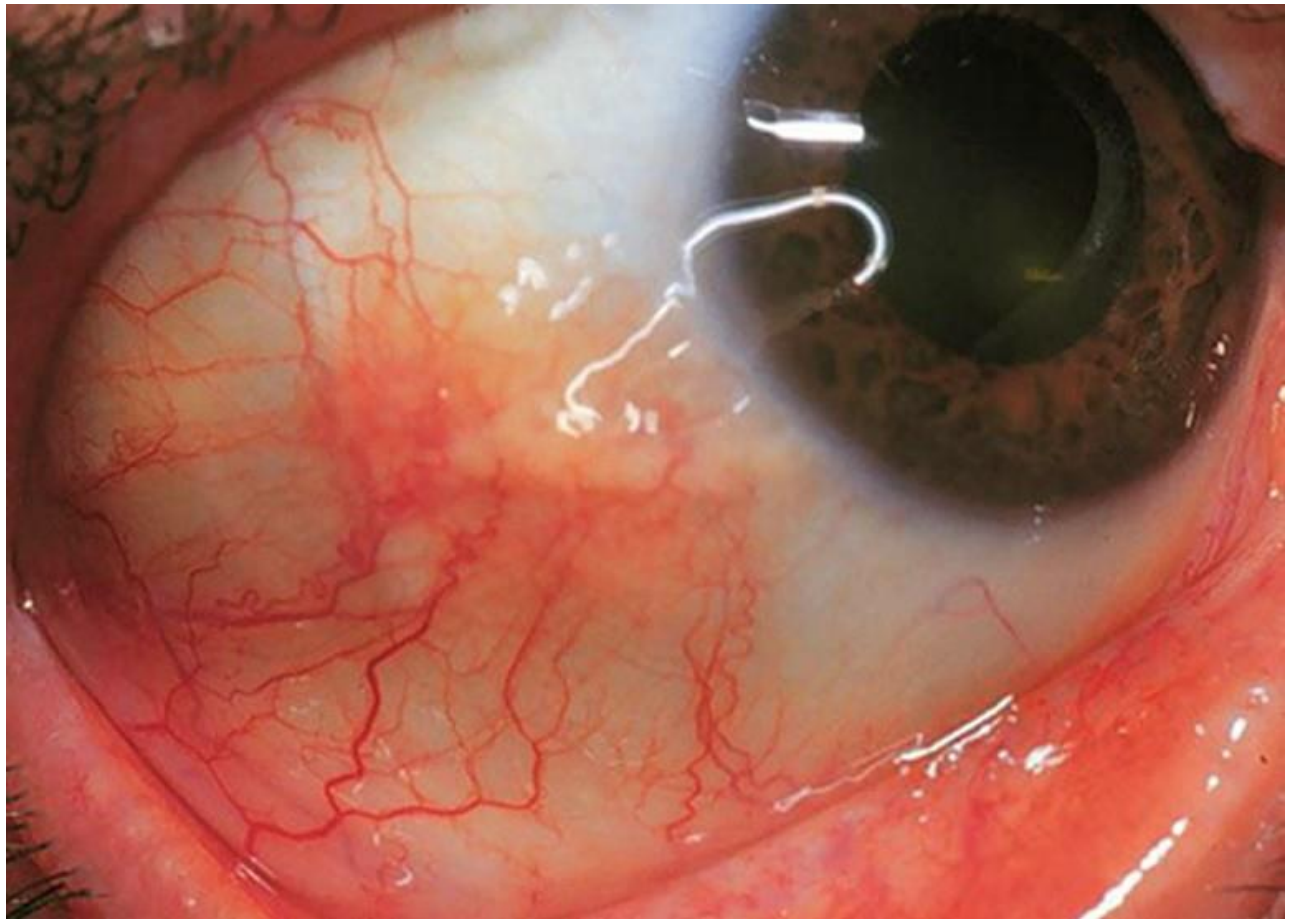
- <1% of overall irAE cases
- 10-12 months after initiation of treatment
- Grade 1: up to 1.5x baseline
- Grade 2/3: 1.5 - 6x baseline
- Full recovery with high dose corticosteroids.
  - (>40 mg/day)

Opthalmolgic irAEs

Opthalmologic irAE presentation

- <1% of overall irAE cases
- Episcleritis
- Uveitis
- Conjunctivitis
- Topical corticosteroids – prednisolone acetate 1%

Opthalmologic irAE presentation



Opthalmologic irAE presentation

Opthalmologic irAE presentation

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Rare irAEs

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Rare irAE presentation

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

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Case Studies

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Case study #1

- 54 year old male with NSCLC

- New immunotherapy treatment initiated 8 weeks ago
- Vision is blurry & sight correction no longer helps
  - Denies eye pain
  - Mild headache “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

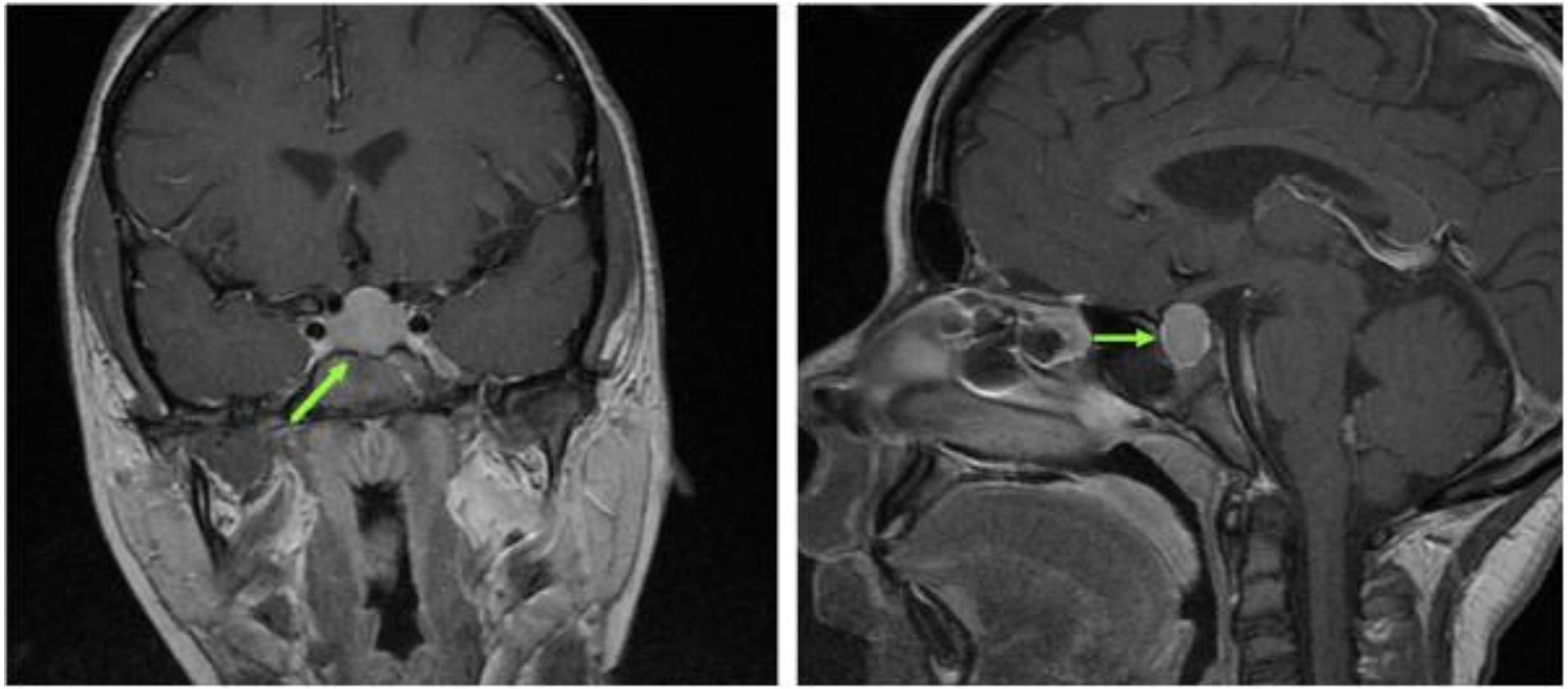
Case study #1

- 54 year old male with NSCLC

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

Case study #1

- 54 year old male with NSCLC



Case study #1

- 54 year old male with NSCLC

- 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

Case study #2

- 45 year old male with NSCLC

- Receiving anti-PD-1 nivolumab for NSCLC
- Diagnosed with hypertension and diabetes
- Symptoms
  - Diffuse abdominal pain for one day
  - Watery, non-bloody diarrhea for three days, >6 stools/day
- Physical Exam
  - Soft, diffuse, mild to moderate abdominal tenderness
  - No rebound or guarding
  - Guaic negative

Case study #2

- 45 year old male with NSCLC

- Plan
  - Contact primary care physician/onc
  - Imaging?
    - CT scan
  - Labs?
    - Stool studies

Case study #2

- 45 year old male with NSCLC

- Diagnosis
  - CT results: Diffuse colitis
  - Stool results: parasites, *C. diff* present

- Treatment
  - Hydration
  - Anagelsia, anti-emetics
  - Antibiotics
  - Steroids

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Further resources

Puzanov *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:95
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Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES **Open Access**

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov[1†], A. Diab[2†], K. Abdallah[3], C. O. Bingham III[4], C. Brogdon[5], R. Dadu[2], L. Hamad[1], S. Kim[2], M. E. Lacouture[6], N. R. LeBoeuf[7], D. Lenihan[8], C. Onofrei[9], V. Shannon[2], R. Sharma[1], A. W. Silk[12], D. Skondra[10], M. E. Suarez-Almazor[2], Y. Wang[2], K. Wiley[11], H. L. Kaufman[12†], M. S. Ernstoff[1*†] and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

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