

ADVANCES IN
Cancer
IMMUNOTHERAPY™



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

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Society for Immunotherapy of Cancer

Disclosures

- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

CTLA-4 and PD-1/PD-L1

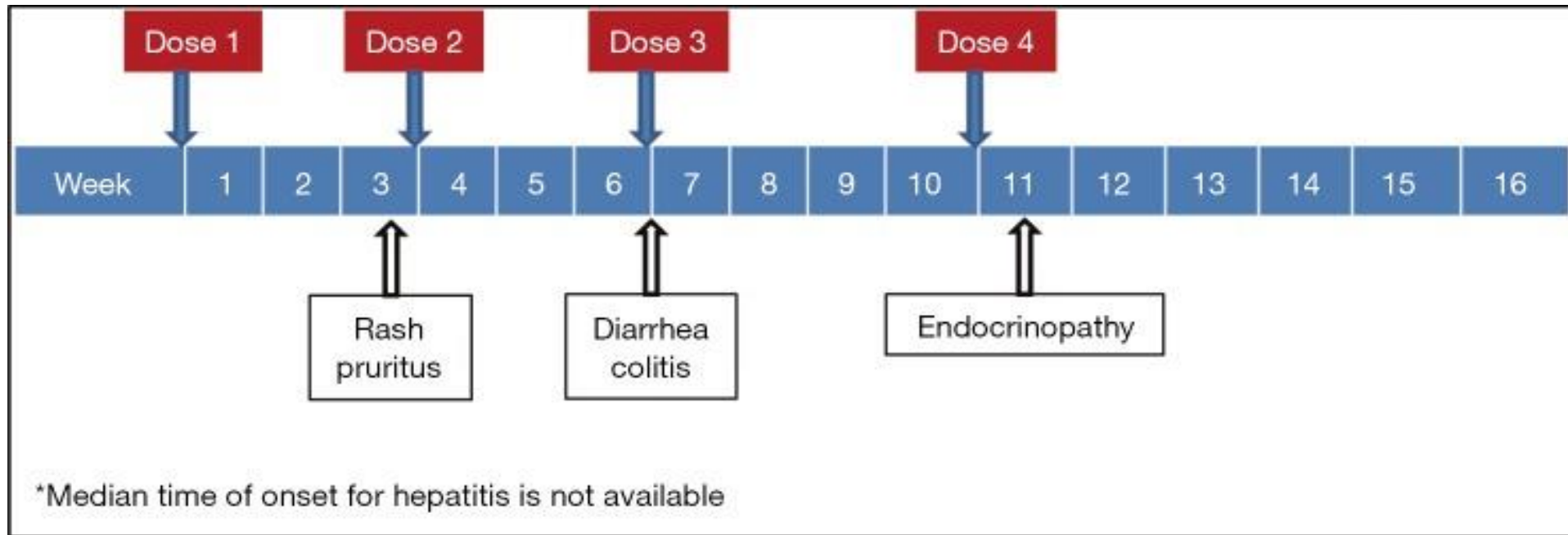
Immune checkpoint mechanisms

- 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

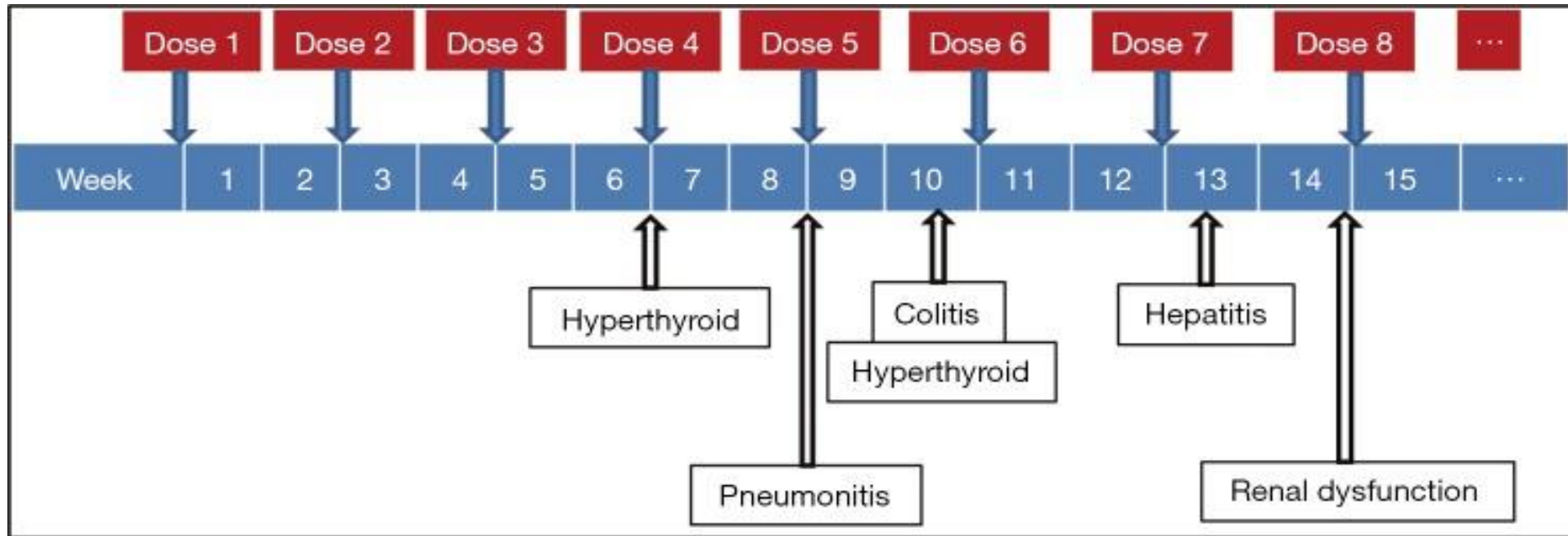
Timing of irAE incidence

- 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

Dermatologic Toxicity

Dermatologic toxicity presentation

- Often presents ~ three weeks post-therapy initiation
- Mild – maculopapular rash with or without symptoms
 - Pruritis, burning, tightness
 - 10% - 30% TBSA
 - Limiting ADL's
 - Topical steroids, hydroxyzine, diphenhydramine
 - Corticosteroids
- 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 permanent
 - No treatment
 - Intra oral lesions – consider candidiasis

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



Vitiligo



Diarrhea/ Colitis

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

Hepatotoxicity

Hepatotoxicity presentation

- 8 -12 weeks after therapy initiation
- Grade 2 toxicity
 - $2.5 < \text{AST/ALT} < 5$ times ULN
 - $1.5 < \text{Bilirubin} < 3$ 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

Endocrinopathies

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

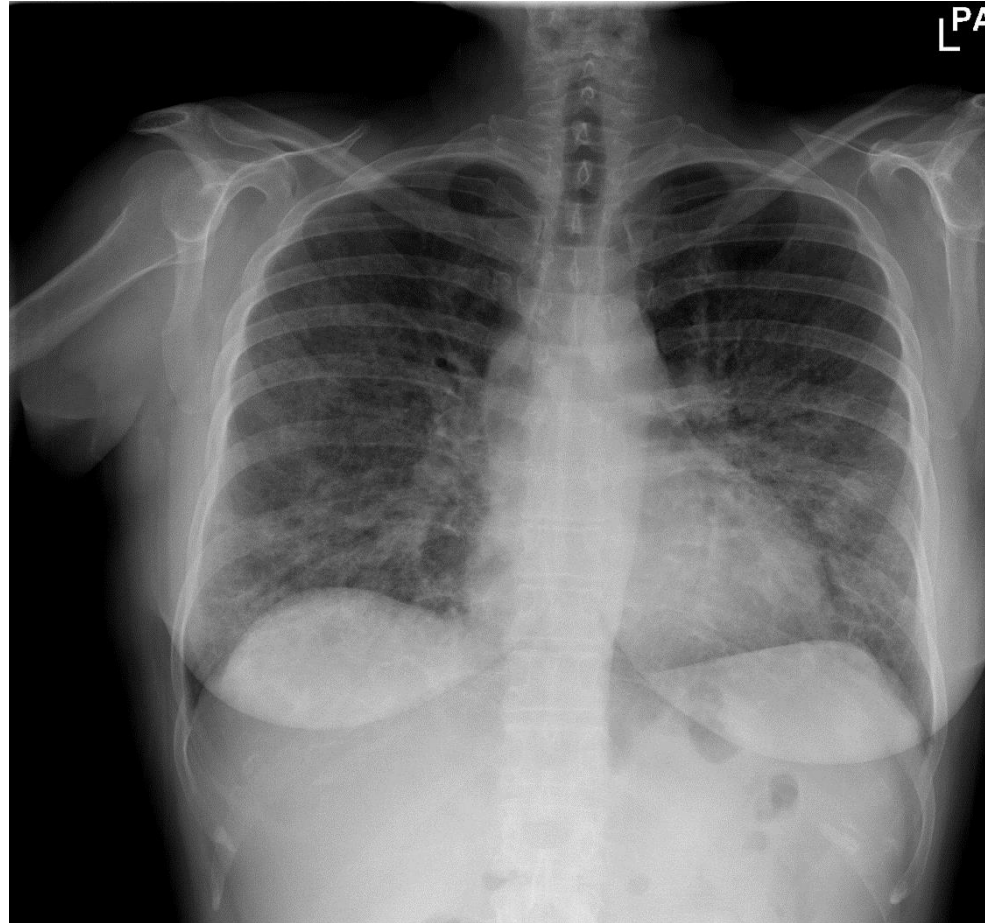
- Hypothyroidism
 - 1 wk-19 months onset after therapy initiation
 - Appropriate levothyroxine replacement
- Hyperthyroidism
 - Check TSH level
 - Acute thyroiditis secondary to immune activation
 - Corticosteroids 1 mg/kg for symptomatic patients
- Adrenal Insufficiency
 - Admission
 - Corticosteroids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

Pneumonitis

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



Pancreatic irAEs

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

Renal insufficiency

Renal insufficiency presentation

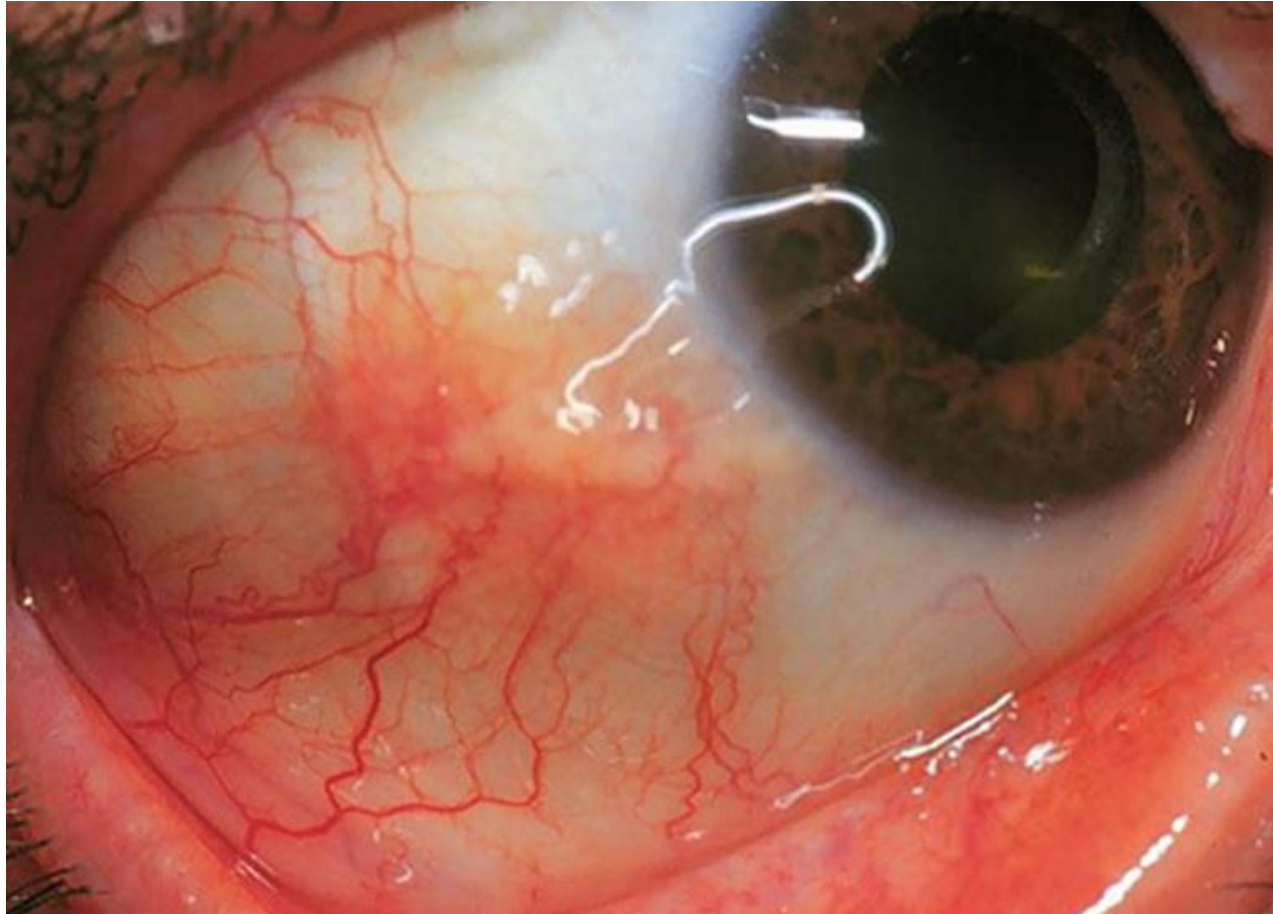
- <1% of overall irAE cases
- 10-12 months after initiation of treatment
- Grade 1: up to 1.5x baseline
- Grade 2/3: 1.5 - 6x baseline
- Full recovery with high dose corticosteroids.
 - (>40 mg/day)

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



Rare irAEs

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
 - ??

Case Studies

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

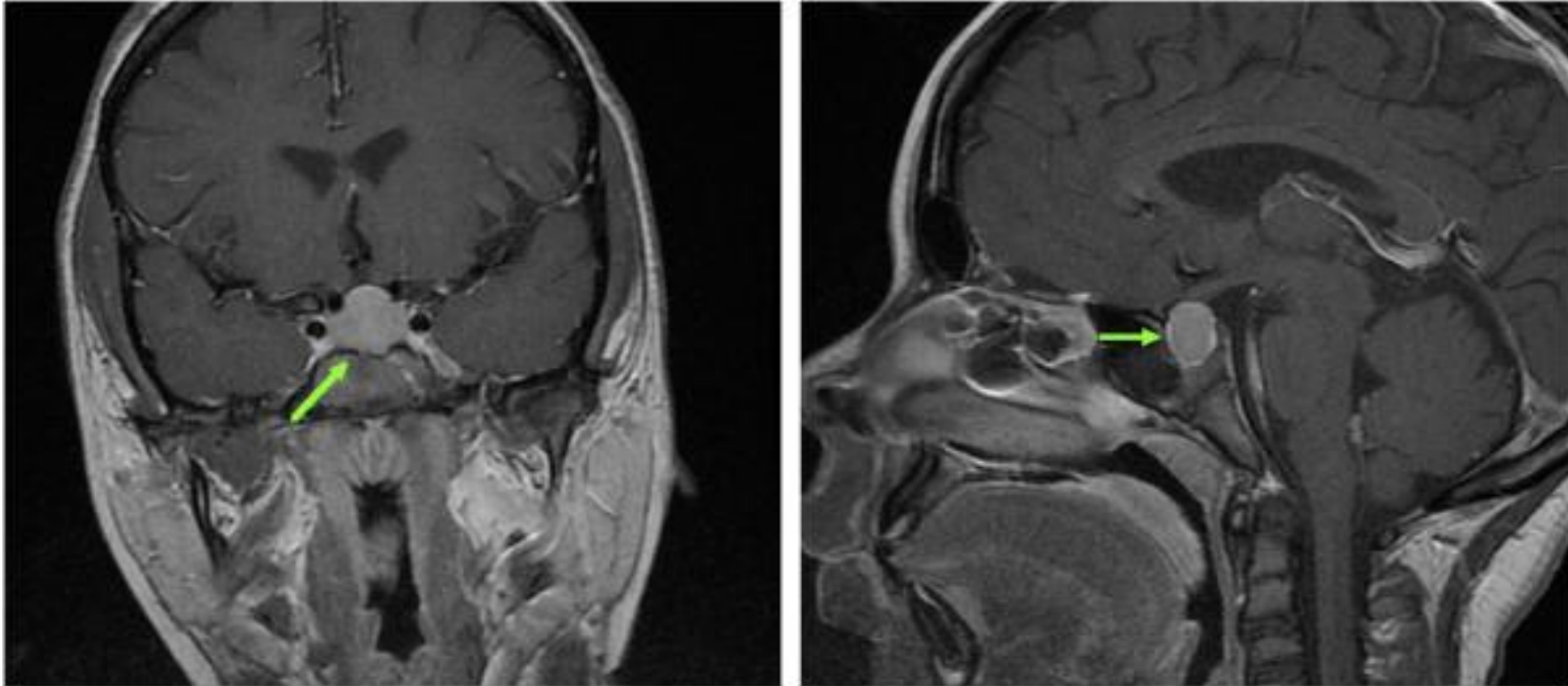
Case study #1

- 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

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

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Y. Wang², K. Wiley¹¹, 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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