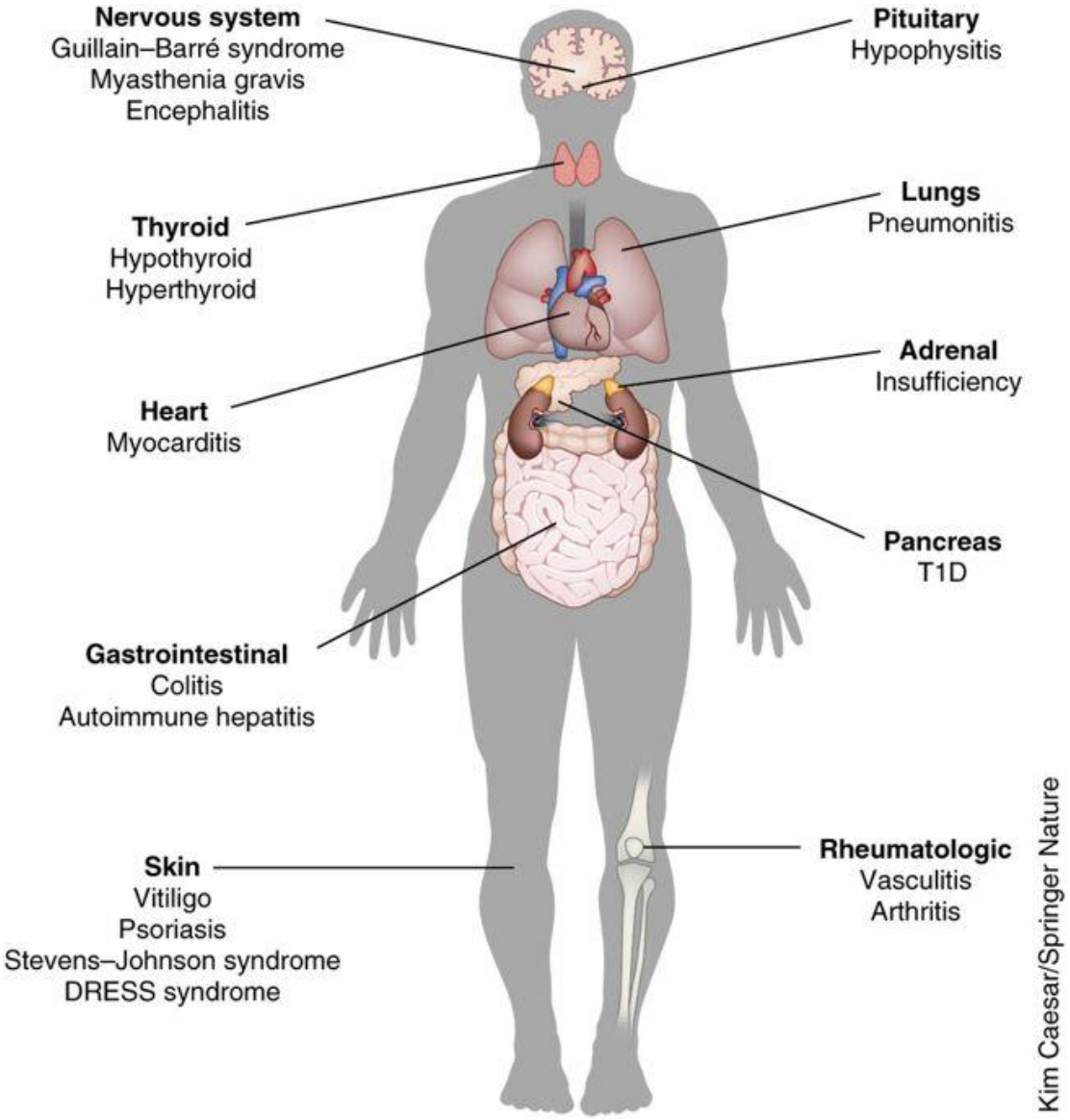
Recognition and Management of Immune-Related Adverse Events

Organ-specific irAEs



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Common Immune Related Toxicities

1. Pneumonitis—Dyspnea, cough, chest pain
2. Colitis—Diarrhea, abdominal pain
3. Hepatitis—Fatigue, abdominal pain
4. Endocrinopathy: Hypophysitis, adrenal insufficiency, hypothyroidism/hyperthyroidism, hypogonadism, diabetes mellitus— Headache, vision change, fatigue, low blood pressure, nausea and vomiting
5. Dermatitis—Rash, itching
6. Nephritis—Fatigue, abdominal pain, leg swelling

Management of Immune Related Adverse Events

- Baseline Labs
  - **Hematology**: CBC with Diff
  - **Electrolytes**: Electrolytes, BUN, Cr, Ca, Mg, Phos
  - **Liver**: ALT, AST, Total Bili, Alk Phos, LDH
  - **Endocrine**: Cortisol, ACTH, TSH, Free T4, Total T3, Glucose, LH, FSH, Testosterone (male), Estradiol (Female)
  - **GI**: Amylase, Lipase
  - **Inflammatory**: ESR, CRP, ANA
  - **TB**: T-spot tuberculosis

Management of Immune Related Adverse Events (Continued)

- **Endocrinopathies**: Cortisol, ACTH, FSH, LH, Testosterone, Estradiol, MRI Brain
- **Diarrhea/Colitis:** Stool studies including c.diff, lactoferrin, calprotectin, CT A/P, colonoscopy + biopsy
- **Pneumonitis**: Sputum culture, respiratory panel PCR, cardiac panel, EKG, 2-D ECHO, 6-minute walk test, complete PFTs, CXR, Chest CT
- **Myositis**: Aldolase, CPK (in addition to baseline labs)

Management of Immune Related Adverse Events (Continued)

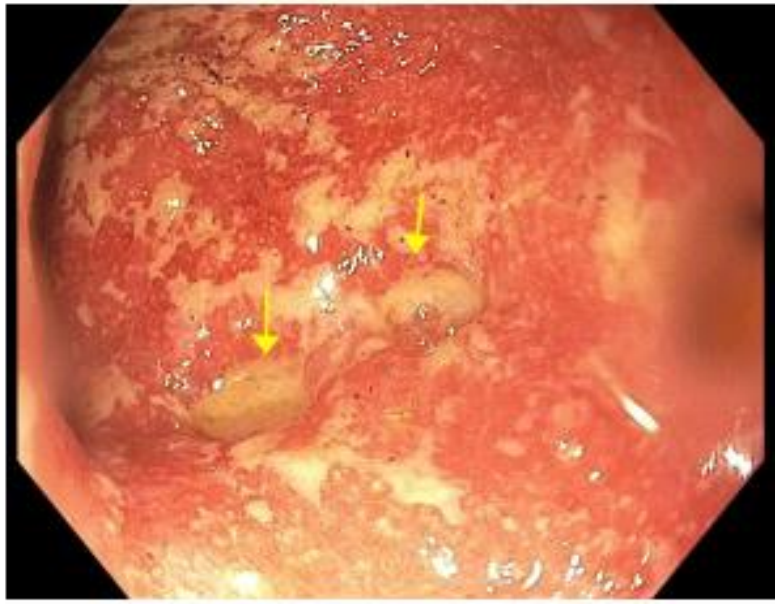
- EARLY DETECTION IS KEY

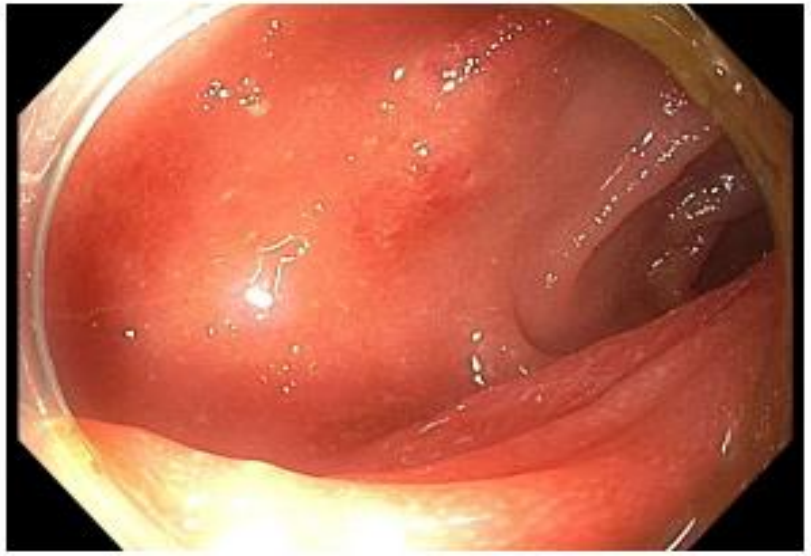
- Corticosteroids (start 1mg/kg BID); infliximab; mycophenolate; tocilizumab

- Colitis considerations:
  - Colonoscopy for biopsy – lymphocytic infiltrate
  - Mesalamine
  - Vedolizumab
  - FMT

Colitis

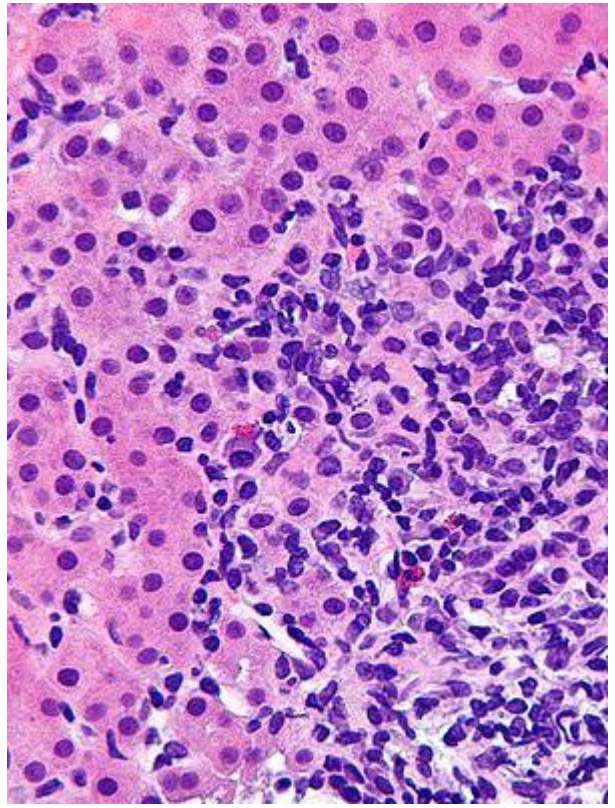
- 71 y/o female with metastatic UTUC on trial with nivolumab/ipilimumab
- After C2, developed profuse watery diarrhea; workup including colonoscopy suggestive of immune colitis
- Failed 3 months of high-dose steroids/taper, infliximab x 2 (TNF blockade), mesalamine, budesonide, vedolizumab (integrin blockade)
- Ultimately had fecal transplant with complete resolution of symptoms





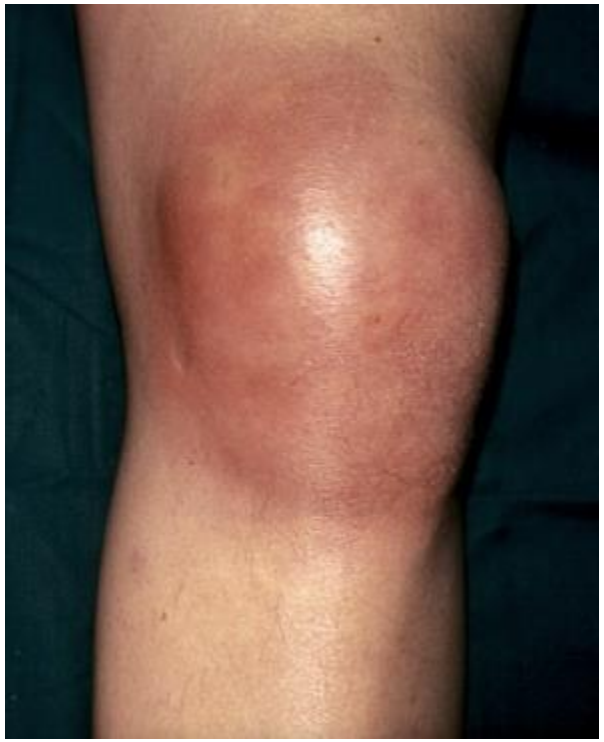
Hepatitis

- 71 y/o male with mRCC, on CheckMate-9ER with cabozantinib + nivolumab
- 6 weeks into therapy, developed Grade 2 transaminitis -> cabozantinib held
- 2 weeks later: ALT / AST in the 800s
- Responded initially to steroids with taper
- Ultimately mycophenolate mofetil considered in absence of resolution



Arthritis

- 74 y/o male with mRCC on nivolumab
- Achieved CR on treatment
- 6 months into treatment, he developed generalized arthralgias, most debilitating in knees
- Responded within hours to low-dose steroids but symptoms returned afterwards, despite slow tapers
- Within 2 months, went from golfing 18 holes to wheelchair bound
- Achieved a gratifying response to tocilizumab (IL-6 blockade)
- Cancer remains quiescent despite 6-month treatment break



Myositis

- 76 y/o M, s/p localized RCC resection enrolled onto clinical trial with adjuvant atezolizumab
- After 3 doses, presented to clinic with mild fatigue, swollen ankles, and achiness
- CK 1217, CK MB 115, Troponin-T 1101
- Muscle biopsy with inflammatory infiltrate
- Treated with steroids, plasmapheresis, rituximab

- Trending cytokine panels, auto-antibodies, SPEP
- Treating T and B cell mediated processes

Myocarditis

- 79 y/o F with mRCC, on nivo/ipi
- Presented with 2-week h/o progressive fatigue, anorexia, shortness of breath
- Workup locally including cardiac catheterization normal
- In ER: somnolent, Troponin T 1800, CK 200, PCO2 92
- Echo with no RWMA
- Intubated, started on steroids, plasmapheresis

- Muscular/neuromuscular AEs can present with overlap syndrome of myasthenia gravis
- Highly morbid
- Treating T and B cell mediated processes
- Biopsies for confirmation of diagnosis -> important to learn but should not hold up empiric treatment

Hypophysitis

- 72 y.o. male with ccRCC with 20% sarcomatoid features w/ mets to LN
- Received with 4 cycles of nivo/ipi on CheckMate 214 trial
- 3 weeks after 4th cycle, he presented w/
  - Nausea & vomiting x 2 days
  - Progressive weakness & fatigue x 2 days
  - Decreased appetite
  - Loss of consciousness, disorientation, and multiple falls x 24 hours

Hypophysitis

- Pt brought to EC
- Hypotensive- BP 86/48 mmHg
- Labs: Na+ 115 mEq/L, K+ 8.8 mEq/L, sCr 2.98 mEq/L
- Glucose 161 mg/dL
- Cortisol 1.8 µg/dL
- Testosterone 28 ng/dL
- TSH 0.34 and free T4 0.62 mU/L

Hypophysitis

- Patient was started immediately on hydrocortisone 1mg/kg Q8H
- MRI brain: NL pituitary gland
- NED from cancer >3 years without any further Rx
- Doing well on glucocorticoid and mineralocorticoid
- Adrenal insufficiency bracelet

Pneumonitis and Hepatitis

- 53 yo WF presented with increasing fatigue, dyspnea, cough and palpable right flank mass
- PMHx: Psoriasis
- CT CAP: 10-cm right renal mass with IVC tumor thrombus, involving the right renal sinus and calyceal system. Scattered bilateral pulmonary nodules and clustered left supraclavicular nodes suspicious for metastatic disease
- Right radical nephrectomy and IVC thrombectomy
  - Pathology: 12.5-cm clear-cell RCC with extension into perinephric adipose tissue, renal sinus, renal vein and IVC; pT3c N0 Mx
- 6 weeks post-op: New and enlarging bilateral pulmonary and liver metastases
  - Hgb = 9.8 g/dL; rest of labs were within normal

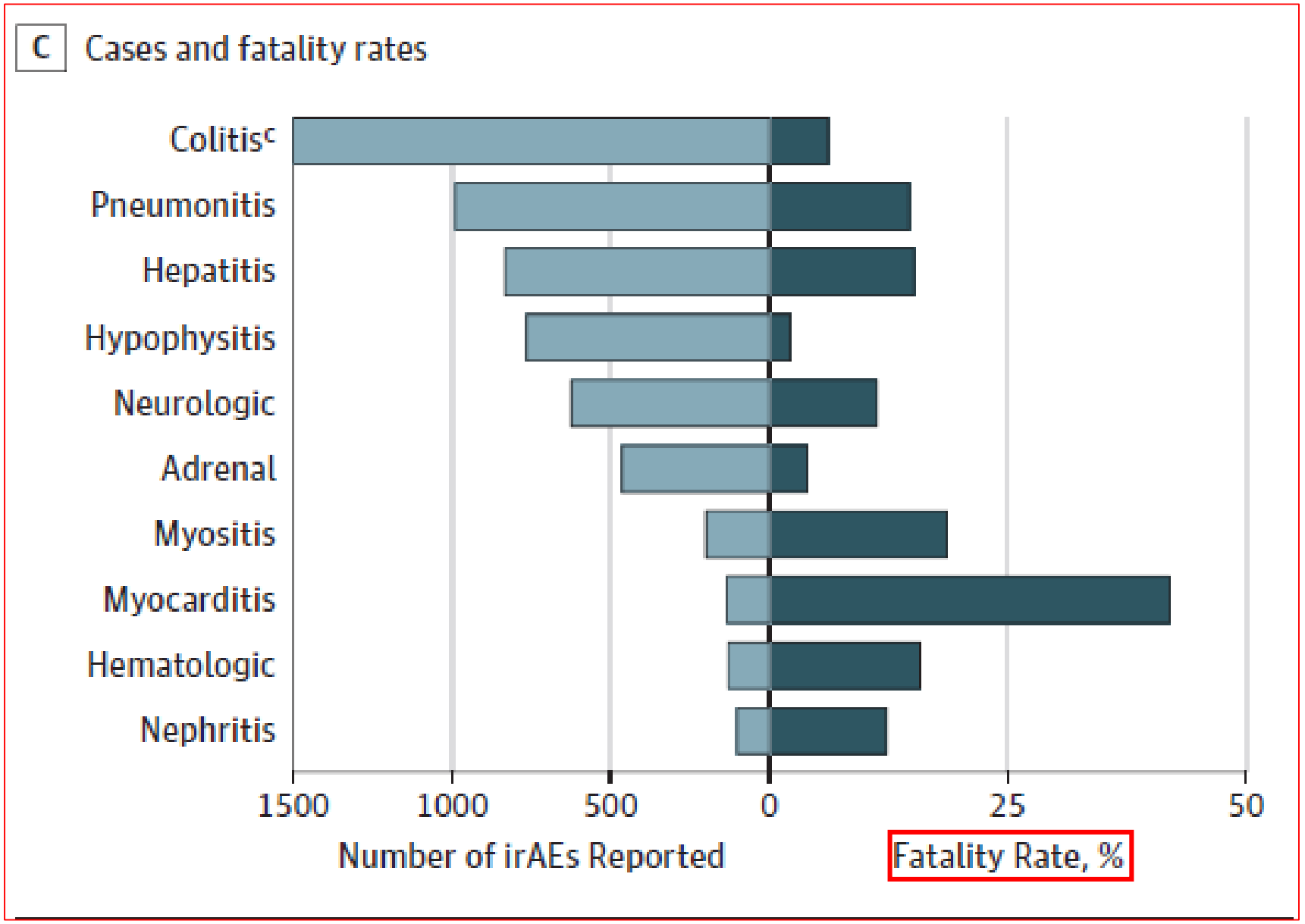
Pneumonitis and Hepatitis

- 7/31/2015: Enrolled on CM 214 and randomized to ipilimumab and nivolumab
- Developed acute thyroiditis after cycle 1
- Hospitalized because of pneumonitis after cycle 2; treated with high-dose corticosteroids with resolution within 6 weeks

Pneumonitis and Hepatitis

- Hospitalized for the 2nd time because of transaminitis (AST 1112 and ALT 1537) and recurrence of pneumonitis
  - Methylprednisolone 1 mg/kg BID restarted
  - She was discharged home on prednisone 100 mg/day with taper of 10 mg/day each week
- Hepatitis and pneumonitis resolved within 6 weeks
- No further immunotherapy administered
- She achieved CR and remains in CR >3 years without any further therapy

Rates of Fatality for Different Types of irAEs



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