Immune-related adverse events due to immune checkpoint inhibitors (ICI)

Lecturer: Dr. Laura Cappelli

Talk Overview:
Diagnosis and management of rheumatic immune related adverse events due to immune checkpoint inhibitors therapy.

Abbreviations: iRAE (immune related adverse events), ICI (immune checkpoint inhibitors), CS (corticosteroids), tx (treatment), pt (patients)

ICI: Currently 7 FDA approved drugs (block CTLA-4 or PD-1/PD-L1) that work by blocking negative costimulatory molecules and increasing activation of T cells

irAE:
- Most irAE have similar symptoms to their rheumatic counterparts with the exception of SLE
- However, irAEs are NOT the same as traditional autoimmune disease
- Significant irAE’s seem to correlate with better tumor responses

Rheumatic irAE
- **Inflammatory arthritis:**
  - Time to development: 1st infusion to >2 years and can continue even after ICI treatment has stopped
  - Sx: medium to large joint involvement (knees most common), tenosynovitis/tendonitis. Axial involvement is rare.
  - Evaluation: elevated inflammatory markers, mostly HLA B27 negative, 90% autoantibody (RF/CCP negative) though some seropositive RA with antibodies even before ICI, joint tap: 3-30K WBC, PMN predominant, imaging: effusions, synovitis, erosions, tenosynovitis, enthesophytes
  - Tx: NSAIDs, IA steroids, corticosteroids, DMARDS: methotrexate, TNF-a inhibitors, tocilizumab
  - Risk factors for persistent arthritis: combination ICI therapy and longer treatment duration
  - Key differences from traditional inflammatory arthritis: fewer + antibodies and not female predominant

- **SICCA syndrome**
  - Time to development: median 70 days from start ICI
  - Sx: Dry mouth more pronounced>>ocular symptoms, only one parotitis report, mucositis
  - Evaluation: decreased salivary flow, positive Schirmer’s, 80-90% seronegative, bx: can have focal lymphocytic sialadenitis as seen in Sjogren’s but can also be different with severe sialadenitis with T cell infiltrate and paucity of B cells with injury to ducts and acini.
  - Tx: saliva substitutes, sialagogues, severe: prednisone taper 20-40mg/day and may get salivary function back
  - Key differences from Sjogren’s: less eye involvement and different pathology

- **PMR/GCA**
  - Sx: shoulder/hip pain/stiffness though some peripheral arthritis can occur before classic PMR symptoms
  - Evaluation: Inflammatory markers, US: subdeltoid bursitis, biceps tenosynovitis, glenohumeral synovitis, hip/synovitis or trochanteric bursitis, TA bx-very important
  - Tx: GCA: 40mg vs high dose IV steroids, PMR: pred 10-60mg, refractory->tocilizumab
  - Key differences
    - PMR: inflammatory markers not always elevated and may need require higher prednisone doses for tx
    - GCA: not associated with aortitis or other large vessel vasculitis

- **Myositis-like**
  - Sx: proximal muscle weakness predominant, diaphragmatic weakness, dysphagia, can overlap with myasthenia gravis and myocarditis (evaluate for these if irAE of myositis)
  - DM: rarer, classic rash on sun exposed areas, Gottron papules, nailfold capillary abnormalities
  - Evaluation: CK (transient high CK with minimal symptoms), EMG: irritable myopathy, MRI with muscle/fascial inflammation, muscle bx: endomysial lymphocytic infiltrate in several reported cases, also necrotizing myopathy
  - Key differences from traditional myositis: rare cases of DM rash and IVIG is less effective

Immunosuppression for irAEs and tumor response- mixed data based on shorter term exposure
- Some studies where CS and TNF-1 did not affect response/survival
- However, hypophysitis (due to ipilimumab for melanoma)tx with high dose steroids had worse survival and baseline CS >10mg associated with worse response in NSCLC

Preexisting autoimmunity and ICIs: ~50% flare, 25-32% de novo irAE