Neurologic Complications of Immunotherapy

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ADULT NEURO-ONCOLOGY PROGRAM
UPMC CANCER REHAB CONFERENCE 2021
Objectives

• Review the most frequently reported ICI-associated neurologic toxicities including clinical features, outcomes and management

• Review various immuno-biologic mechanisms that have been proposed to explain why certain patients might develop neurologic irAEs

• Inform providers who care for patients with cancer of the common neurologic irAEs to improve recognition and prompt evaluation and consultation with appropriate specialists.
Cancer Immunotherapy

- Immune checkpoint molecules expressed on T cells, B cells and Natural Killer cells regulate inflammatory and autoimmune responses.
- Generalized immune activation leads to tumor suppression and may also lead to autoimmune adverse events.

Cancer Immunotherapy

- Tumors express inhibitory ligands PD-L1/PDL-2 and B7-1/B7-2
- These ligands interact with receptors PD-1 and CTLA-4 on T cells to downregulate T cell responses – “OFF Switch”
- Immune checkpoint inhibitors (ICIs) prevent T-cell CTLA-4 or PD-1 from binding to tumor CD80/86 and PD-L1
- Leads to inhibition of the ‘inhibitory’ co-stimulatory interactions between T cells and tumor cells, resulting in positive signals – “ON Switch”
Cancer Immunotherapy

- ICIs prevent CTLA-4 or PD-1 from binding to their receptors – inhibits the inhibitory co-stimulatory interaction between T-cells and tumor
- Leads to positive co-stimulation and uncontrolled T cell activation

Cancer Immunotherapy

- Enhanced Th1 and Th-17 responses and cytokine production (IL-6, IL-17) leading to abnormal Treg function
- Altered Treg/Th17 function thought to be critical for development of autoimmune disease.

Commonly Used ICIs

- CTLA-4: Ipilimumab
- PD-1: Pembrolizumab, Nivolumab
- PD-L1: Atezolizumab, Avelumab, Durvalumab
Case Report

- 65M with metastatic melanoma BRAF WT stable brain metastases s/p L frontal resection and post-op SRS
- Treated with 4 cycles ipilimumab/nivolumab followed by 8 cycles nivolumab monotherapy
  - Pruritis and diarrhea
- 1-week history of recurrent fevers, generalized weakness, fatigue, unwitnessed fall with LOC, progressive lethargy and obtundation
Case Report

- ED Course: T39.7, HR 120, RR34; CXR clear, UA negative, blood cultures negative, CTH stable post-op changes, started on empiric IV antivirals/antibacterials
- CT C/A/P: no evidence of new metastatic disease, no infectious processes
- MRI brain: lack of T2 flair suppression without abnormal enhancement
- EEG: Delta activity, maximal left frontotemporal and diffuse theta activity
- LP: WBC 10, lymph 92%, glucose 53, protein 38
Case Report

• Serum Labs Negative:
  • CPK 34
  • Lactate 1.6
  • CRP 0.6
  • RPR nonreactive
  • TSH 1.943
  • Paraneoplastic panel
  • RVP
  • Autoimmune encephalitis panel
  • ANA, SSA/SSB, RF, dsDNA,

• CSF Studies Negative:
  • Autoimmune encephalitis panel (GAD, purkinje cell antibody, amphiphysin, antineuronal antibody, CRMP5, AMPA, VGKC, glutamine decarboxylase)
  • AFB, cryptococcus, toxoplasmosis
  • Culture, fungal
  • HSV1/2, VZV, CMV, EBV, WNV
  • Cytology negative for malignant cells
Case Report

- Hospital Days 1-3: progressive lethargy and obtundation
  - Repeat CTH stable, repeat EEG focal slowing
- Intervention: 1mg/kg Prednisone x 5 days
- Response: Rapid improvement within 24 hours
- Prednisone Taper: 90mg/day x 1 week, 70mg/day x 1 week, 60mg/day x 1 week, then continued to decrease by 10mg/day each week until off.
- Follow-up: return to baseline (neurological examination, MMSE, MRI Brain) by 4 weeks. 5-month follow-up remains neurologically stable.
Neurologic Complications in Patients Treated with ICIs

- Neurologic complications of ICI
- Neurologic complications of other cancer treatments (e.g., chemotherapy, XRT)
- Neurologic complications of cancer (e.g., cord compression)
- Paraneoplastic neurologic syndromes
ICI-Associated Neurologic Complications

• Resulting from enhanced T cell activation can affect nearly every organ with varying degrees of severity (e.g., colitis, hepatitis, pneumonitis, autoimmune retinopathy, uveitis, etc.)

• ICI-associated neurological complications can occur at any point during ICI administration (even after completion), but 60–80% occur within the first 4 months of therapy initiation

• Incidence ranges from 2-4%

• Mild events (e.g., headaches, dizziness, paresthesias) that do not impact ICI continuation seen in 6-12% of patients

• More serious events < 1%
  • 0.4% to 0.2% with nivolumab and pembrolizumab
  • 0.3–0.8% with ipilimumab
  • 2.4–14% with the combination of PD-1 and CTLA-4 inhibitors
Relative Frequency of ICI-Associated Neurologic Complications

• Vigibase Database: Neurologic irAEs after ICI
  • Autoimmune Encephalitis and/or Myelitis 250
  • Neuromuscular syndromes (Myasthenia Gravis) 228
  • Guillain Barre Syndrome (AIDP) 122
  • Aseptic meningitis 72
  • Mononeuropathies 42
  • Cerebral vasculitis 34
  • Chronic polyneuropathies 23
ICI-Associated Autoimmune Encephalitis

• Often occurs within *first few days or weeks* of ICI treatment in about 0.1-0.25% of patients (especially in combined CTLA-4/PD1)

• Can occur up to 297 days after initial treatment

• Varied clinical presentations

• Antineuronal antibodies may be elevated (e.g., Hu, NMDA-R)

• Treatment
  • Stopping ICI
  • High dose corticosteroids +/- IVIG
ICI-Associated Autoimmune Encephalitis

- Defined as inflammatory condition of the brain caused by an immune mediated response against the brain parenchyma
- Acute to subacute onset (less than 3 months) rapid progression of working memory deficits, altered mental status or psychiatric symptoms
- Exclusion of well-defined syndromes of autoimmune encephalitis
- Absence of well-characterized autoantibodies in serum or CSF
- At least one of the following:
  - New focal CNS findings
  - Seizures (new onset)
  - CSF pleocytosis (> 5 cells per mm3 in WBC) or CSF-specific OCBs and/or elevated CSF IgG index
  - MRI features suggestive of encephalitis
  - Reasonable exclusion of alternative causes
ICI-Associated Aseptic Meningitis

• Occurs within first 1–7 weeks after ICI initiation and occurs in approximately 0.1–0.2% of patients.
• CSF shows lymphocytic pleocytosis
• MRI may show meningeal enhancement
• Most respond to steroids
ICI-Associated Hypophysitis

• Occurs in upwards of 5-10% within 6-12 weeks after initiation
  • Median onset 76 days; usually after 3 cycles
• Presents with headache, fatigue, dizziness, endocrine deficiencies (ACTH, TSH)
  • More likely to occur with CTLA-4 blockade or combination (3.2 and 6.4% vs 0.4% with PD-1)
• Serum level of pituitary hormones is low and MRI Brain may show enhancement and swelling of the pituitary gland
• Responds to high-dose steroids along with long-term hormonal supplementation
ICI-Associated Myasthenia Gravis

- 0.12% of all patients treated with immunotherapy (~1 in 800)
- Almost always within 3 months from starting ICI (7-10 weeks after initiation); typically with Pembrolizumab or Nivolumab
- 77% with new onset of MG, 23% with exacerbations
- 93% generalized MG, 70% with AChR-seropositive MG
  - No cases of MuSK-MG reported so far
ICI-Associated Myasthenia Gravis

- Commonly associated with overlap myositis (in as many as 47% cases)
  - Worse prognosis if associated with myocarditis
- Variable severity and clinical course
  - Some patients may improve spontaneously, other develop generalized myasthenia and myasthenic crisis
- Acetylcholine receptor antibody testing and repetitive stimulation may be negative
- Can evolve rapidly at all stages of these treatments, even after completion
- Responds well to corticosteroids, IVIG or plasmapheresis
ICI-Associated Inflammatory Myopathies

• Median onset – 26 days
• Serum CK typically above 1000, with frequent overlap syndromes and unusual variants (e.g. orbital myositis manifesting with ptosis or eosinophilic fasciitis)
• Histopathology – variable, from necrotizing and inflammatory myopathies to nonspecific biopsy findings with little or no signs of muscle inflammation
• Necrotizing autoimmune myositis (most common), dermatomyositis, polymyositis,
ICI-Associated Inflammatory Myopathies

- **Puwanant** (n=38) – 37% with MG/myositis overlap (n=14);
  - 82% with CK>1000, 37% with CK>5000
- **Moreira** (n=38) – 38% with myocarditis
- **Anquetil** (n=180; Vigibase)
  - 15.6% with MG; 16.1% with myocarditis; 3.3% with both myocarditis and MG
- **Seki** (n=19) – ptosis as initial manifestation in 53% of patients
  - 84% with CK >1000; 68% with striated muscle abs
ICI-Associated Peripheral Neuropathies

- Occur in < 1%
- 74% occurs within 3 months from starting ICI
- Risk 5-fold greater with combination of CTLA-4 and PD-1/PD-L1 inhibitors
- Varying severity
  - Inflammatory demyelinating polyradiculoneuropathies (AIDP/CIDP) occurring in 0.1-0.2%
  - small-fiber sensory type (as commonly seen with chemotherapies, not affecting the continuation of ICIs)
  - Polyradiculopathy
  - Mononeuritis multiplex
  - Cranial neuropathies

Neurology 2019. doi:10.1212/00000000008091
ICI-Associated Peripheral Neuropathies

- Most patients improve with corticosteroids
- MRI often shows spinal root enhancement
- Cranial neuropathies may accompany meningitis !!
- CSF often shows high protein content and elevated WBC count
  - 38% with WBC >50 in CSF, 56% with protein >100 and 30% with protein >200 mg/dl
- Anti-nerve antibody titers rarely elevated
ICI-Associated Overlap Neuromuscular Syndromes

• Very uncommon in “wild type” patients
• Most common overlap of myasthenia gravis and myositis
  • Worse outcomes with myocarditis
• Many patient have other systemic autoimmune complications (e.g. vitiligo, colitis ...)
• Unusual overlaps of neuropathy-myositis-myasthenia gravis (!)
ICI and Preexisting Autoimmune Disease

- Can lead to disease exacerbation in 27-38% patients with underlying inactive autoimmune disorders (i.e., severe exacerbation of multiple sclerosis during ipilimumab therapy)
- Risk prediction for subclinical inflammatory disease remains active question
ICI and Paraneoplastic Disease

• Theoretically can promote immune-mediated paraneoplastic syndromes due to cross-reactivity and molecular mimicry from both neural and tumor cells

• Treatment with anti-CTLA-4 antibody induces inflammation of Purkinje cells in mice as seen with paraneoplastic cerebellar degeneration

• A phase 2 trial found anti-Hu and anti-Yo antibodies detected in 45% patients with SCLC treated with ipilimumab

• Paraneoplastic complications evolve slowly and do not fit the temporal profile of the ICI-associated neurological disorders; by contrast, the ICI-associated autoimmune neurological diseases evolve rapidly and occur at all stages of ICI treatments, even after completion
Possible Mechanisms of irAEs

- Epitope sharing
  - Cross-reaction inducing T effector cell activation against self-tissues
- Epitope spreading
  - Teff-cell-mediated tumor cell death in the cancer-microenvironment causes the release of a huge amount of tumor antigens and self antigens
- Direct toxicity
- Flares of pre-existing autoimmune disorders
Autoantibody Detection

- **Myasthenia Gravis** – 70% acetylcholine receptor seropositive
  - no reports of MuSK generalized myasthenia to date
- **Inflammatory Myopathies** – myositis-specific antibodies relatively rare
  - up to 68% have elevated titers of striated muscle antibodies
- **Autoimmune Encephalitis** - rare
- **Paraneoplastic Syndromes** – rare
  - Pre-treatment serum samples may show elevated autoantibody titers prior to immune checkpoint blockade and symptom onset
    - Question of false positive versus autoimmune tendency
Systemic and Neurologic Complications

- 58% patients with myositis or peripheral neuropathy also had systemic irAE
Clinical Work-Up

There are no biological and clinical markers pathognomonic for ICI-related neurologic disorders. The differential diagnosis remains the most informative component in the stepwise approach to a patient in whom ICI-associated irAE is strongly suspected on clinical grounds.

First objective is to exclude other possible causes (progression of oncological disease, infectious, metabolic, autoimmune, paraneoplastic, or other neuro-muscular syndromes).
Clinical Work-Up

• Any grade 3 symptoms should prompt urgent neurological consultation
• Testing – similar evaluation as non-ICI neurologic syndromes
  • **Meningoencephalitis** – MRI brain, CSF studies, serology
  • **GBS/CIDP** – EMG/NCS, CSF studies, consider spinal MRI (+/- contrast)
  • **Myasthenia gravis** – AChR and MuSK serology, CK, rep stim and/or SFEMG, NIFs/VC
  • **Myopathy** – CPK, transaminases, LDH, aldolase, cardiac enzymes, ESR, CRP, A-ChR antibodies, EMG/NCS, consider muscle biopsy, consider brain MRI (re: orbital myositis) or limb MRI (re: biopsy guidance), serology for myositis specific antibodies
Treatment

- Balance between treatment of cancer and autoimmune complications
  - Consider withdrawal or change of immune checkpoint inhibitors
  - Immunosuppression may diminish efficacy of cancer immunotherapy
Treatment

- **Hold/Stop ICI for severe complications**

- **Corticosteroids**
  - Oral prednisone 0.5-1.5 mg/kg/day or IVMP pulse 1 g/day x 5 days

- **For patients with GBS/MG/meningoencephalitis** – consider IVIG 0.4g/kg/day x 5 days or PLEX
  - May combine with corticosteroids

- **In aggressive, non-responsive disease, off-label treatment should be considered**
  - Abatacept 500–1000 mg every two weeks
  - Rituximab 375 mg/m2 per week x 4 weeks
  - Methotrexate, azathioprine, mycophenolate mofetil
Emerging physician awareness

Diagnostic complexity

Inconsistent awareness across patients

Lack of widespread evidence

Johnson et al., Lancet 2020
UPMC Neuro-Oncology Approach
Symptom – Diagnosis – Treatment

**Symptom Severity**
- **Mild**: No significant disability despite symptoms; able to carry out usual activities
- **Moderate**: Requires some help, but able to walk without assistance
- **Severe**: Unable to walk and attend to bodily needs without assistance

**Diagnostic Work-up**
- **Neurological Examination**
  - Serum Labs: CBC, CMP, HbA1c, TFTs, B12/folate, HIV, RPR, Lyme, ESR/CRP, CPK, Autoimmune Screen
- **MRI Brain +/- Spine w/wo contrast**
  - Lumbar Puncture (cytology, OCBs, IgG index, Viral PCRs, Autoimmune Encephalitis/Paraneoplastic Panel
  - Serum paraneoplastic panel +/- EMG/NCS

**Treatment**
- **Monitor symptoms closely**
  - Continue immunotherapy, low threshold to discontinue if progression
- **Hold immunotherapy**
  - Neuro-oncology consult
  - Empiric antibiotics/antivirals (meningoencephalitis coverage)
  - Initial observation OR consider corticosteroids
- **Discontinue immunotherapy**
  - Neuro-oncology consult
  - Empiric antibiotics/antivirals (meningoencephalitis coverage)
  - Initiate corticosteroids (prednisone 1mg/kg/day)
Discussion

- Prompt diagnosis, discontinuation of ICIS, early corticosteroid treatment, and multidisciplinary approach are important for optimizing neurological recovery.
- Routine diagnostic work-up may be unremarkable.
- Corticosteroid taper may be insufficient to produce durable neurological stabilization or recovery.
- Unanswered questions regarding risk factors for development of IRAEs.
- Uncertainty regarding decision to stop or re-initiate treatment with immune checkpoint inhibitors.
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