Grave Toxicities of Immune Checkpoint Inhibitors

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Learning Objectives

1. Develop a differential for respiratory failure in a patient receiving ICI therapy
2. Recognize and empirically treat the triad of irAE myocarditis, myositis, and myasthenia gravis

Case

HISTORY OF PRESENT ILLNESS

A 75-year-old man with metastatic renal clear cell carcinoma presented with dyspnea 26 days after receiving cycle 1 of ipilimumab and nivolumab.

ONCOLOGIC HISTORY

3/2006: Clear cell renal cell carcinoma diagnosis. L radical nephrectomy.
3/2008: Solitary pulmonary metastasis. Wedge resection.
3/5/16: Subcarinal lymph node recurrence. 6000 cGy radiotherapy.
4/2022: PET avid subcarinal lymph node.
4/6/22: R occipital recurrence. Resection and 2700 cGy radiotherapy.
2/2023: Nivolumab/Ipilimumab cycle 1.

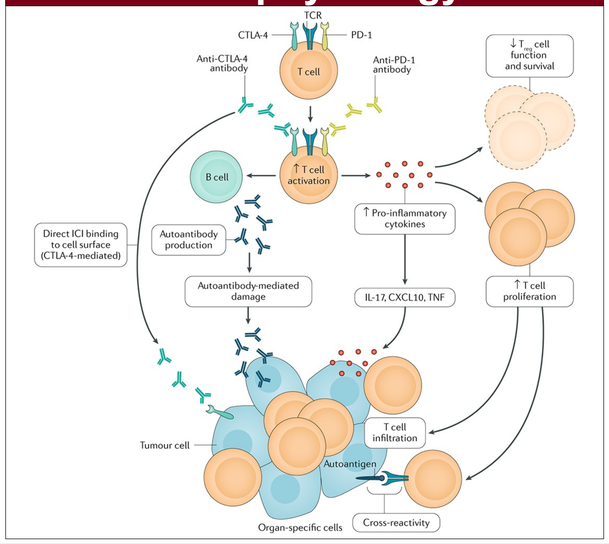
EXAM

Tachypnea, accessory muscle use, hypoxia requiring 2 liters of oxygen

INITIAL LABS & IMAGING

- Troponin 2.99, CPK 610, BNP 641.
- ECG: T-wave inversions in the inferior and septal leads
- CT chest: bibasilar infiltrates and a previously seen subcarinal mass newly invading and partially occluding the right mainstem bronchus

Pathophysiology

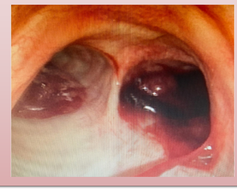


Clinical Course

HD1 Admission
- Started methylprednisolone 1000mg daily
- MG testing sent
- TTE: no WMA, EF 45-50%

HD3
- Intubation for progressive hypercapnic respiratory failure.
- NIF was -9 suggestive of diaphragmatic weakness
- Started mycophenolate 1000mg twice daily
- Cardiac MRI unattainable

HD4-5
- Bronchoscopic debulking
- Passed SBT, extubated, reintubated within 24h



HD6
- Started plasma exchange

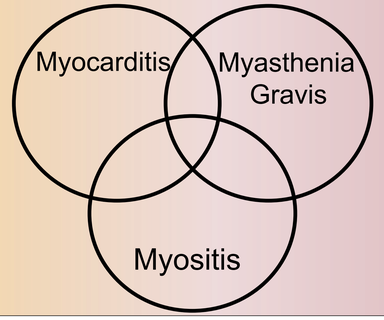
HD9
- AChR and striated muscle antibodies resulted positive
- Started pyridostigmine
- Medications reviewed for MG exacerbators

HD10
- Progressive multiorgan dysfunction despite 5 days of PLEX
- Transitioned to comfort care

Differential, Evaluation, & Management

Hypoxic

Pneumonitis



Guillain-Barre Syndrome

Hypercapnic

	Pneumonitis	Myocarditis	Myositis	Myasthenia Gravis	GBS
Workup	• Labs: Blood/sputum cultures • CT chest • BAL • Lung biopsy	• Labs: Troponin, CPK, BNP, viral PCR/serology • ECG & telemetry • TTE • Stress test • Cardiac MRI • Cardiac Cath +/- Biopsy	• Strength and skin exam • Labs: CPK, Aldolase, AST, ALT, LDH, ESR, CRP, urinalysis • Musculoskeletal MRI • EMG • Muscle biopsy • Autoantibody testing – Anti TIF1gamma, Anti NXP)	• Antibody testing: AChR, anti-striated muscle, MuSK, LPR4 • PFTs (NIF, VC) • MRI brain if bulbar weakness to evaluate for leptomeningeal disease	• MRI spine • Lumbar puncture • Autoantibody testing: ANNA-1 antibody, antiganglioside antibody, anti GQ1b • EMG • PFTs (NIF, VC)
1st line	Steroids 1-2mg/kg/day	Steroids 1000mg/day	Steroids 1-2mg/kg/day	Steroids 1-2mg/kg/day	PLEX and/or IVIg
Other	• Infliximab • MMF • IVIg • Cyclophosphamide (not NCCN) • Tocilizumab (only SITC)	• MMF • Infliximab (unsafe in CHF) • ATG • Abatacept • Alemtuzumab • Other: CHF GDMT, Pacemaker	• PLEX and/or IVIg • Biologics – Rituximab, Infliximab • Tocilizumab (only ASCO) • Immunosuppressants – MTX, AZA, MMF	• PLEX and/or IVIg • Rituximab • Other: pyridostigmine, avoid MG exacerbating drugs, daily PFTs	• Steroids 1000mg/day (SITC)

Takeaways

- ASCO, NCCN, and SITC guidelines suggest many potential therapeutic options based on anecdotal evidence, therefore clinical gestalt is essential in determining the appropriate initial workup and 2nd line therapy
- The differential for acute respiratory failure in the setting of ICI therapy includes:
  1. Pneumonitis
  2. The 3M triad - Myocarditis, Myositis, and Myasthenia gravis
  3. Guillain-Barre Syndrome
- A high clinical suspicion for these diagnoses allows for:
  - Early initiation of high dose steroids 1000mg/day
  - A broad initial diagnostic workup
  - Empiric treatment that addresses multiple etiologies
  - Avoidance of MG triggering medications

References

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