Neuromuscular irAE’s & ‘Triple-M Syndrome’

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Neuromuscular irAE’s

• Immune-related neuromuscular irAEs are rare, but potentially life-threatening
• Occur in 1-5% of patients
• Can occur as a syndrome encompassing multiple organs, including myocarditis
• Increased incidence with dual ICB
• Known risk factors are limited (hx of autoimmune disease)

Martins et al. Nature 2019
Neuromuscular irAEs

• The burden of NMirAE's is not just immediate
• High rates of chronic manifestations, with significant impact on QOL
Myositis

- Overall incidence is <1% of all patients, but estimated MC neurologic irAE
- Typical onset is within 5-6 weeks
- Symptoms can be variable and progress quickly
  - Muscle pain/weakness
  - Head drop, ptosis
  - Life-threatening if respiratory/bulbar involvement
- Elevated **CK, EMG changes**, antibodies are often negative

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Jordan et al J ESMO Open 2021
Alsaleh et al Current Oncology 2023
Myasthenia Gravis

- IrAE MG frequently overlaps with myositis and other irAEs
- More fulminant than idiopathic cases, with >50% having respiratory or bulbar weakness
- Acetylcholine receptor autoantibodies can be seen, but not in all cases

Table 1. Clinical findings in neuromuscular immune-related adverse events

<table>
<thead>
<tr>
<th>Clinical findings in NMD induced by ICI</th>
<th>Myasthenia gravis</th>
<th>Myositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular weakness</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Facial weakness</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Bulbar symptoms</td>
<td>+++</td>
<td>+ ++ 50% of the cases</td>
</tr>
<tr>
<td>Extremity weakness</td>
<td>+ Symmetrical proximal</td>
<td>+ Symmetrical proximal</td>
</tr>
<tr>
<td>Dropped head</td>
<td>++</td>
<td>++ ++ 70% of the cases</td>
</tr>
<tr>
<td>Limb girdle weakness</td>
<td>++/++</td>
<td>++</td>
</tr>
<tr>
<td>Pain</td>
<td>(+)</td>
<td>++ ++ 70% of the cases</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Frequent due to diaphragm involvement or aspiration</td>
<td></td>
</tr>
<tr>
<td>Reflexes</td>
<td>Normal</td>
<td>May be reduced according to paresis</td>
</tr>
<tr>
<td>Cardiac pathology</td>
<td>Rare in isolated MG, 10% overlapping myositis-myoarditis</td>
<td>++ 25%-35% myocarditis, arrhythmia</td>
</tr>
</tbody>
</table>

Additional findings

- Laboratory findings: CK Normal, elevated in myositis overlap Markedly (fivefold to 10-fold) elevated (including troponin) up to 100x, rarely normal
- Cerebrospinal fluid: Normal Normal
- Antibody status: May be positive for AChR, often negative or very low titres Negative

Jordan et al J ESMO Open 2021
Myositis/Myasthenia Gravis Treatment

- Most patients will respond to high dose IV steroids
- IVIG and/or plasma exchange may be needed – low threshold to initiate if worsening symptoms
- Other treatments can include abatacept, mycophenolate, azathioprine, rituximab
- Prolonged treatment is often required
- In most cases, ICB will need to be permanently discontinued
Myocarditis

• Rare – but very high mortality (~50%)
• First reported incidence of 0.09% in safety data -> more recent registry data = 1.1%
• Can occur in up to 30% of irMyositis
• Meta-analysis of 22 studies:
  • CHF = 2.0%
  • MI = 1.0%
  • Cardiac arrest = 1.0%

Ball et al JAAC 2019
Myocarditis diagnostic criteria

IC-OS 2021 Consensus
Either pathohistological diagnosis:
Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples
Or clinical diagnosis:
A troponin elevation (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline)
with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion

Major Criterion
• CMR diagnostic for acute myocarditis (modified Lake Louise criteria)

Minor Criteria
• Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgia, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock)
• Ventricular arrhythmia and/or new conduction system disease
• Decline in cardiac (systolic) function, with or without regional WMA in a non-Takotsubo pattern
• Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis
• Suggestive CMR (meeting some but not all of the modified Lake Louise criteria)
Assessment/Management

**Initial Management:**
- Permanently discontinue immunotherapy
- Management is tailored to response and acuity of presentation
- High-dose steroids such as methylprednisolone pulse dosing 1 g/d IV for 3-5 days
  - If responding and stable, switch to oral prednisone (1 mg/kg/d), then taper slowly over 6-12 weeks based on clinical response and improvement of biomarkers

**Myocarditis Workup:**
- Complete history and physical examination
- Second ECG and cardiac biomarkers
- TTE
- cMRI ± endomyocardial biopsy
- Neuromuscular assessment
  - Myostis-myasthenia gravis syndrome (CPK, AChR)
  - Rule out ACS
    - Coronary angiogram or CTA

**Consistent with definite/probable/possible myocarditis?**
- Yes
  - Complete methylprednisolone 1 g IV daily x 3 days
  - 12-lead ECG if rhythm changes on telemetry
  - Daily cardiac biomarkers to assess for treatment response
- No
  - If no improvement within 24-48 hours on steroids, consider further interventions:
    - Abatacept
    - Mycophenolate
    - Intravenous immunoglobulin (IVIG)
    - Alemtuzumab
    - Infliximab (use with extreme caution in patients with reduced LVEF)
    - Antithymocyte globulin (ATG)
    - Plasmapheresis
    - ICU-level monitoring
    - Temporary or permanent pacing as required

**Evaluate other causes**
- No

Lehmann et al JAMA Cardiology 2021
NCCN Clinical Practice Guidelines
Conclusions

• Neuromuscular irAE's and Triple M syndrome carry high rates of morbidity and mortality
• Although rare, non-specific symptoms may lead to underdiagnosis
• Rapid identification and appropriate intervention can be life-saving!
• Close monitoring and multidisciplinary evaluation (neurology, cardiology) are needed
• Guidelines from national organizations provide excellent resources for initial management (SITC, ASCO, NCCN, ESMO etc)