Neurologic complications of checkpoint inhibitors?

• Occur in less than 5% of treated patients
• Reported conditions
  – Transverse myelitis
  – Neuropathy
  – Encephalitis
  – Myositis
  – Myasthenia gravis

Review of Myositis

• A heterogeneous family of autoimmune diseases targeting skeletal muscle
• Usually associated with extramuscular manifestations (skin, lung, joints, etc…)
• Major types: dermatomyositis, polymyositis, and necrotizing autoimmune myositis
• ~80% have a myositis-specific autoantibody
• Increased risk of cancer (e.g., ~25% of dermatomyositis patients)
Overview of Myasthenia Gravis

• Autoimmunity targeting components of the neuromuscular junction

• Two major types defined by autoantibodies (found in 85% of patients)

• Anti-AChR autoantibodies
  – 80-95% of those with generalized MG
  – 50% of those with ocular MG

• Anti-MuSK autoantibodies
  – 50% of anti-AChR negative patients

• 15% of MG patients have thymoma
  – 99% with thymoma are anti-AChR+
Case report

Myasthenia triggered by immune checkpoint inhibitors: New case and literature review

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Table 1
Published cases of immune checkpoint-inhibitor-associated myasthenia gravis (MG).

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Treatment/Infusion</th>
<th>Cancer</th>
<th>AChR serology (pre/post)</th>
<th>Serum CK (IU/L)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5]</td>
<td>IPI (3rd)</td>
<td>MEL</td>
<td>ND/+</td>
<td>ND</td>
<td>CS + PLEX</td>
<td>Stable (IPI stopped, on prednisone)</td>
</tr>
<tr>
<td>[5]</td>
<td>IPI (2nd)</td>
<td>MEL</td>
<td>ND/+</td>
<td>ND</td>
<td>CS</td>
<td>Fatal (cancer, IPI stopped)</td>
</tr>
<tr>
<td>[6]</td>
<td>IPI (2nd)</td>
<td>MEL</td>
<td>ND/+</td>
<td>1200</td>
<td>CS + PLEX + IVIG</td>
<td>Stable (IVIG, IPI stopped)</td>
</tr>
<tr>
<td>[7]</td>
<td>NIV + IPI (1st)</td>
<td>SCLC</td>
<td>ND/+</td>
<td>ND</td>
<td>PLEX + IVIG + CS</td>
<td>Fatal (withdrawal of care during myasthenic crisis)</td>
</tr>
<tr>
<td>[8]</td>
<td>NIV (1st)</td>
<td>MEL</td>
<td>+/+</td>
<td>7740</td>
<td>PLEX + IVIG + CS</td>
<td>Stable (treated for myasthenic crisis)</td>
</tr>
<tr>
<td>[9]</td>
<td>NIV (3rd)</td>
<td>MEL</td>
<td>ND/+</td>
<td>1627</td>
<td>None</td>
<td>Spontaneous resolution of MG</td>
</tr>
<tr>
<td>[10]</td>
<td>NIV (3rd)</td>
<td>NSCLC</td>
<td>ND/+</td>
<td>ND†</td>
<td>CS</td>
<td>Stable (nivolumab stopped)</td>
</tr>
<tr>
<td>[12]</td>
<td>PEM (5 weeks)</td>
<td>MEL</td>
<td>+/ND</td>
<td>ND</td>
<td>IVIG + CS</td>
<td>Stable (pembrolizumab stopped; on prednisone)</td>
</tr>
<tr>
<td>[13]</td>
<td>PEM (3rd)</td>
<td>MEL</td>
<td>+/−</td>
<td>ND</td>
<td>PLEX + IVIG + CS</td>
<td>Stable</td>
</tr>
<tr>
<td>Ours</td>
<td>PEM (4th)</td>
<td>CarSar</td>
<td>ND/−</td>
<td>1200</td>
<td>CS</td>
<td>Stable (pembrolizumab continued, on prednisone)</td>
</tr>
</tbody>
</table>

* Mildly elevated (exact value not available).
† Elevated transaminases.

PEM – pembrolizumab; NIV – nivolumab; IPI – ipilimumab; ND – no data; MEL – melanoma; NSCLC – non-small cell lung carcinoma; SCLC – small cell lung carcinoma; CarSar – carcinosarcoma; MG – myasthenia gravis; PLEX – plasma exchange; CS – corticosteroids; na – not applicable.
• 12 cases of MG
• 3 IPI, 4 NIV, 4 PEM, 1 IPI + NIV
• 8/11 Anti-AChR+
• 3 with prior h/o MG
• No thymomas
• CK levels elevated in all 6 patients tested
Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan

- 9869 received nivolumab; 408 received ipilimumab
- 28% with immune adverse events
- 1.7% with neurologic immune adverse events
- 12 cases (0.12%) of MG with nivolumab
- 10 of 12 were low titer anti-AChR+
  - 3 positive before treatment; 1 with known h/o MG
- Weakness occurred 29 +/- 13 days post-Rx
- At least 4 had myositis (maybe 7), 3 had myocarditis, and 1 had both
- Weakness was severe in 8
- 2 patients died
- In rest, immunosuppressive therapy was effective

Suzuki et al., Neurology, 2017
Avelumab in recurrent thymoma

- 7 patients with thymoma and 1 patient with thymic carcinoma treated at NIH (James Gulley)
- None with prior h/o myositis or MG
- 4 of 7 developed high CK levels and weakness
- Peak CK levels (762 to 16,037 IU/L) reached 7 to 35 days after avelumab
- All 4 were anti-AChR+ after treatment
  - One tested before and was AChR+ positive
- None had myositis autoantibodies before or after
- Immunosuppressive therapy was effective
  - One had recurrent CK elevations and weakness
- Myositis/MG was associated with favorable tumor response

Mammen and Rajan, et al, unpublished
Immunophenotyping of PBMCs: Low B cell count prior to avelumab may be associated with developing myositis/MG.
Low B cell count prior to avelumab is associated with developing myositis/MG.
Avelumab study team

- Arun Rajan
- James L. Gulley
- Jeffrey Schlom
- Renee N. Donahue
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- Livia Casciola-Rosen
- Christopher R. Heery
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Conclusions

• Myositis and MG occur in ~1 in 1000 patients treated with checkpoint inhibitors.
• Myositis and MG often appear together (this is rare in those not receiving checkpoint inhibitors).
• In ~1/3 of cases, myocarditis occurs along with myositis/MG.
• ~50% of thymoma patients treated with avelumab develop myositis/MG.
  – Low B cell levels may predict susceptibility to myositis/MG in these patients.