Cancer Immunotherapy-Associated Myositis and Myasthenia Gravis

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Neurologic complications of checkpoint inhibitors?

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

Hottinger AF, Curr Opin Neurol 2016;29:806-812.
Friedman CF, JAMA Oncol 2016;2:1346-1353.

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+

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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).

Ref.	Treatment/Infusion	Cancer	AChR serology (pre/post)	Serum CK (IU/L)	Treatment	Outcome
[5]	IPI (3rd)	MEL	ND/+	ND	CS + PLEX	Stable (IPI stopped, on prednisone)
[5]	IPI (2nd)	MEL	ND/+	ND	CS	Fatal (cancer, IPI stopped)
[6]	IPI (2nd)	MEL	ND/+	1200	CS + PLEX + IVIG	Stable (IVIG, IPI stopped)
[7]	NIV + IPI (1st)	SCLC	ND/+	ND	PLEX + IVIG + CS	Fatal (withdrawal of care during myasthenic crisis)
[8]	NIV (1st)	MEL	+/+	7740	PLEX + IVIG + CS	Stable (treated for myasthenic crisis)
[9]	NIV (3rd)	MEL	ND/+	1627	None	Spontaneous resolution of MG
[10]	NIV (3rd)	NSCLC	ND/+	ND†	CS	Stable (nivolumab stopped)
[11]	NIV (1st)	MEL	+/+	8729	Declined	Fatal (myasthenic crisis)
[4]	PEM (3rd)	MEL	ND/−	Elevated*	CS + PLEX	Fatal (cancer)
[12]	PEM (5 weeks)	MEL	+/ND	ND	IVIG + CS	Stable (pembrolizumab stopped; on prednisone)
[13]	PEM (3rd)	MEL	+/−	ND	PLEX + IVIG + CS	Stable
Ours	PEM (4th)	CarSar	ND/−	1200	CS	Stable (pembrolizumab continued, on prednisone)

* 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.

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- 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

Suzuki et al., Neurology, 2017

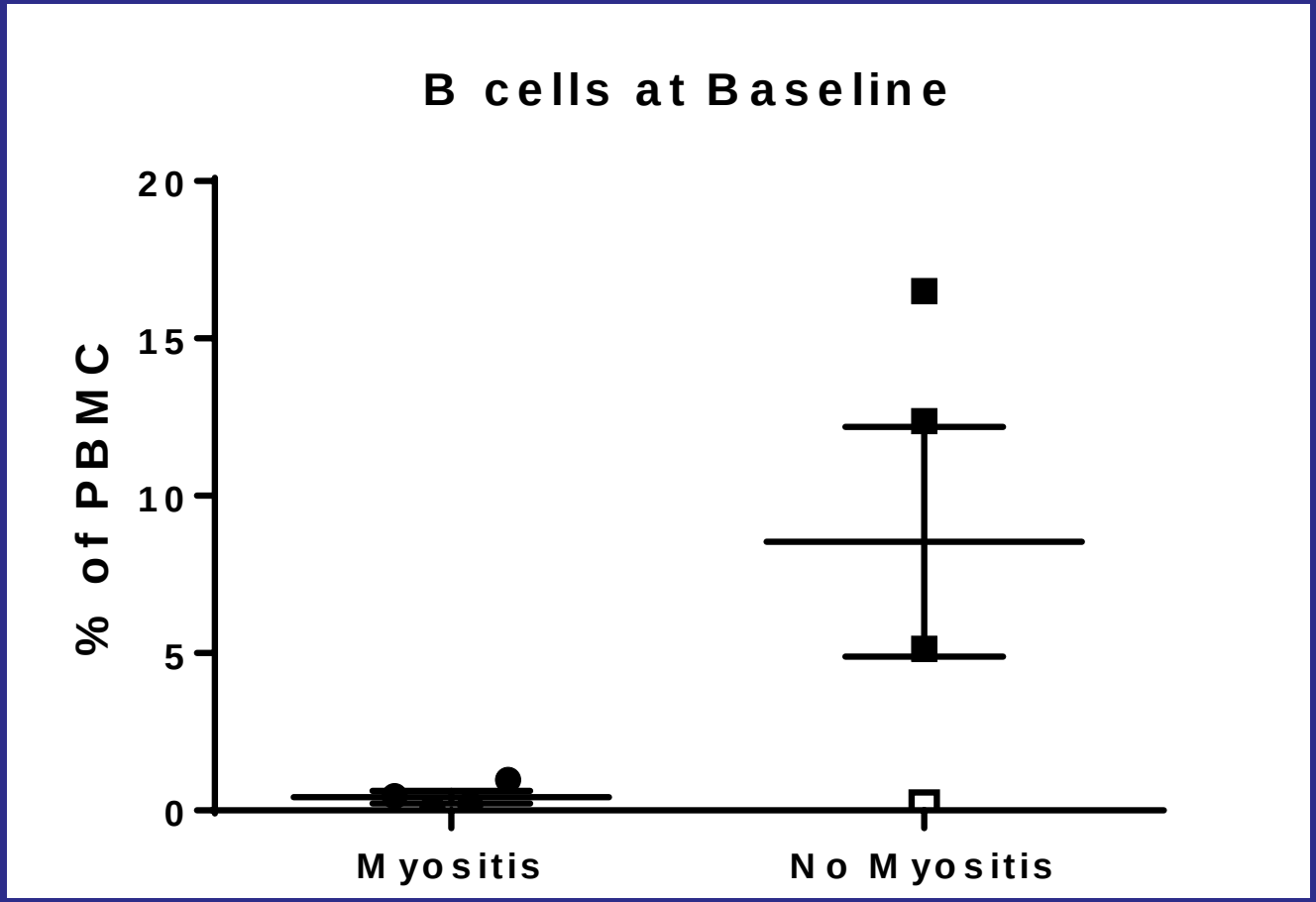
- 9869 received nivolumab; 408 received ipilimumab
- 28% with immune adverse events
- 1.7% with neurologic immune adverse events
- 12 cases (0.12%) of MG with nivolumab
- 10 of 12 were low titer anti-AChR+
  - 3 positive before treatment; 1 with known h/o MG
- Weakness occurred 29 +/- 13 days post-Rx
- 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

Avelumab in recurrent thymoma

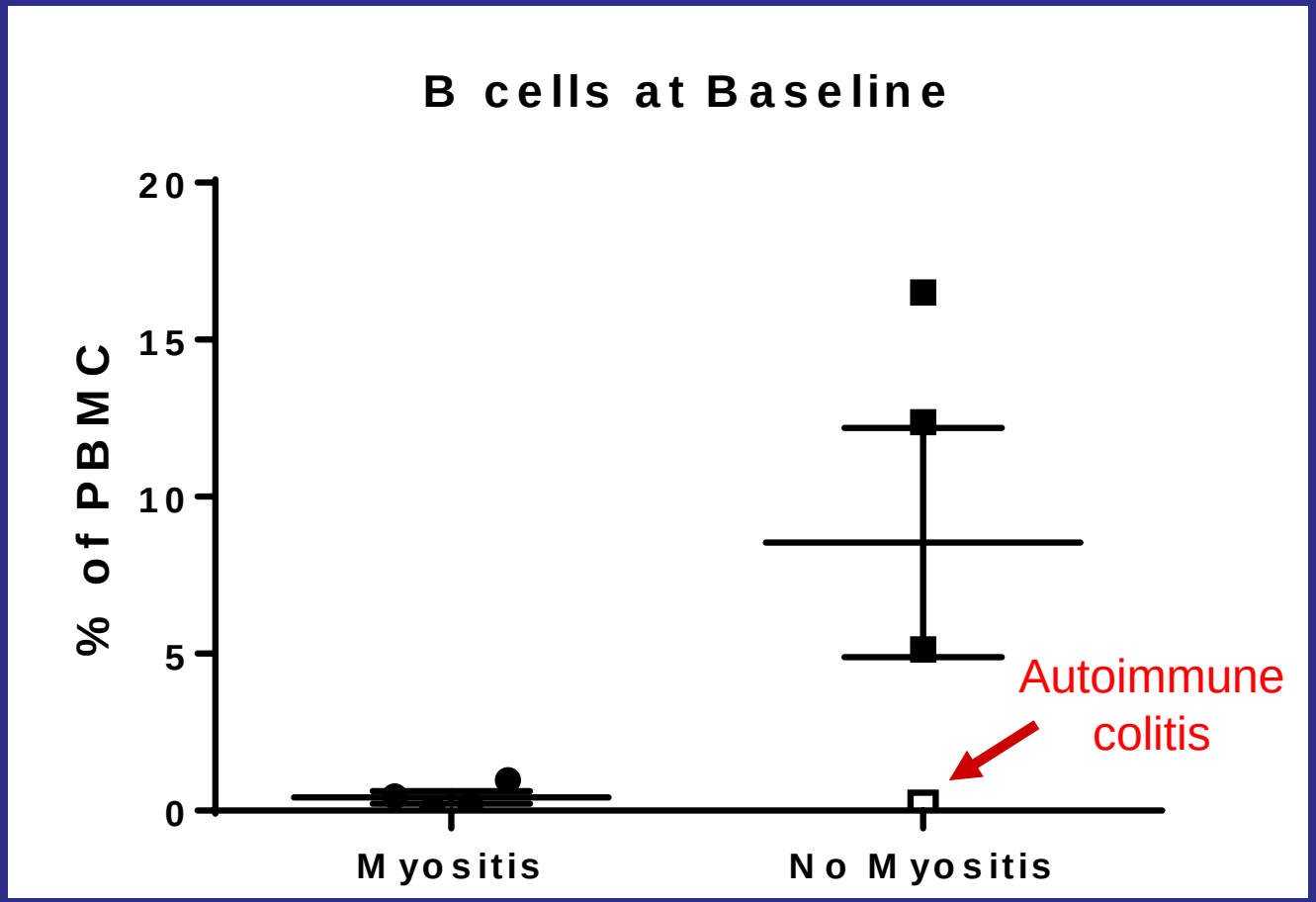
- 7 patients with thymoma and 1 patient with thymic carcinoma treated at NIH (James Gulley)
- None with prior h/o myositis or MG
- 4 of 7 developed high CK levels and weakness
- Peak CK levels (762 to 16,037 IU/L) reached 7 to 35 days after avelumab
- All 4 were anti-AChR+ after treatment
  - One tested before and was AChR+ positive
- None had myositis autoantibodies before or after
- Immunosuppresive 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
- Tanya Lehky
- Livia Casciola-Rosen
- Christopher R. Heery
- Lauren M. Lepone
- Kevin Chin
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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