Case Presentation: Pembrolizumab-induced myasthenia gravis in a 73 year-old man

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Case Presentation

A 73 year-old man with past medical history significant for hypertension, hyperlipidemia, obstructive sleep apnea, atrial fibrillation, and active history of metastatic renal carcinoma presented due to concern for progressive bulbar weakness and impending respiratory failure. Patient developed sensation of muscle aching and soreness, extremity numbness and tingling, and paresthesias 2 weeks prior to arrival. He was evaluated by ENT, Hematology/Oncology, and Neurology at an outside hospital due to aforementioned symptoms then transferred to Ochsner with the onset of progressive dysphagia. Immunotherapy-related autoimmune dysphagia was the working diagnosis, leading the primary team to hold his current oncologic treatment which included axitinib and pembrolizumab. He denied a history of similar complaints previously as well as a personal or family history of autoimmune disease.

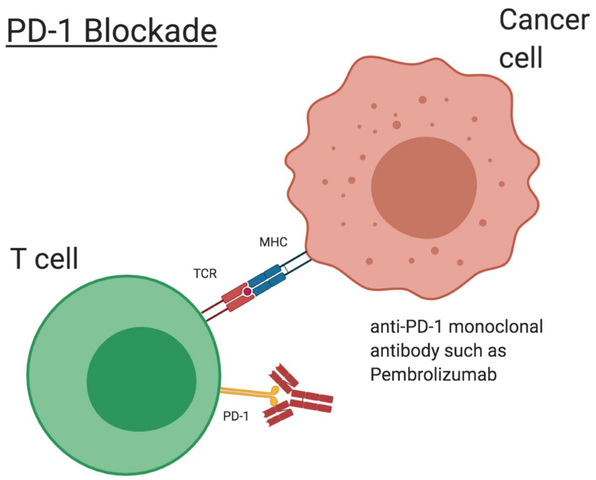
ENT examination and laryngoscopy at bedside was unremarkable. Decision was made to observe patient in the Neuro Critical Care Unit due to progression of his symptoms, with worsening weakness of neck flexion and extension leading to concern for patient at risk for needing possible intubation. Initial neurologic examination demonstrated bilateral ptosis with sustained upgaze, activation of frontalis muscles to attempt to open eyes more fully, and weakness on neck flexion and extension. Strength was intact aside from musculoskeletal pain limiting range of motion of the left upper extremity. Vital Capacity of 2.2 L. Negative Inspiratory Force was -35. Decision was made to initiate treatment and intubation was ultimately avoided.

During hospitalization patient received a 5 day course of IV Ig followed by methylprednisolone 70 mg every 12 hours with improvement in symptoms. Patient was started on pyridostigmine 30 mg every 6 hours for some residual bulbar weakness. This medication was subsequently held due to excessive respiratory secretions. Lab work up was notable for positive anti-striated muscle antibodies and titin antibody. After completing his IVIg treatment, patient was transferred to an MD Anderson as this institution has developed a protocol for monoclonal antibody-induced complications including myasthenia, myositis, and myocarditis. Clinical improvement was notable on discharge–slightly nasal and hoarse voice, decrease in secretions, decreased ptosis, and normal strength in extremities were noted on last exam.

Per record review, patient was discharged from MD Anderson, with most of his oculomotor and bulbar weakness resolved.

Pembrolizumab Mechanism of Action

Pembrolizumab, along with nivolumab and cemiplimab, are anti-PD1 antibodies, which act to augment the immune response to cancerous cells. Programmed cell death 1 receptor can bind to ligands on tumor cells to inhibit T cell response via negative feedback. This increase in immune response has been the proposed mechanism by which pembrolizumab causes myasthenia gravis among other known autoimmune adverse drug effects such as pneumonitis, colitis, and endocrinopathies.



Literature Review

Trial	Age/Sex	Symptom Onset	Antibodies	Symptoms
Tedbirt et al.	*77 yo M*	*After 4th infusion*	*AChR -, MuSK -*	*Vision changes, ptosis, dysphagia*
March et al.	*63 yo M*	*After 1st infusion*	*AChR +, MuSK -*	*Ptosis, blurred vision, SOB, death s/p withdrawal of care*
Zhu and Li	*59 yo F*	*After 3rd infusion*		*Hoarseness, dysphagia, DOE, generalized weakness*
Lau et al.	*75 yo M*	*After 1st infusion*		*Difficulty walking, neck weakness, ptosis*
Zimmer et al.	*69 yo F*	*After 3rd infusion*	*AChR -*	*Bulbar weakness, ptosis, SOB, death*
Algaeed et al.	*73 yo M*		*AChR binding +*	*Ptosis, SOB, neck flexion, generalized weakness*
Phadke et al.	*67 yo M*	*After 3rd infusion*		*BLE weakness*
	75 yo M	*After 2nd infusion*	*AChR +*	*Dysphagia, DOE, limb weakness, diplopia, ptosis*
Gonzalez et al.	*71 yo F*	*After 4th infusion*	*AChR -, MuSK -*	*Dysphagia, diplopia, dysarthria*

Conclusions

New onset myasthenia gravis and exacerbation of existing myasthenia gravis is the most common neuromuscular side effect of pembrolizumab. Careful work up is required as symptoms can be similar to inflammatory myositis which is another common adverse effect of pembrolizumab. Approximately 70% of patients will have side effects on these types of monoclonal antibodies and ~1% of these side effects are neurologic in nature. Myasthenia gravis is a rare, but potentially fatal side effect of pembrolizumab and requires high index of suspicion in a patient developing weakness. Many patients do well with neurologic and oncologic treatment. New onset or exacerbation of myasthenia gravis is not an absolute contraindication to continued use of immune checkpoint inhibitors and there are cases where patients have been restarted on these therapies with careful management of myasthenic symptoms. Collaboration of oncology and neurology in these cases is crucial to optimizing patient care. Future directions could include implementing models similar to MD Anderson's protocol for dealing with known complications such as myasthenia and myositis to ensure appropriate monitoring and precautions are in place.

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