Neurologic complications in cancer patients exposed to checkpoint inhibitors

Michael N. Youssef1, Rebecca A. Harrison2, Karin Woodman3, Merry Chen1
1Department of Neurology, Baylor College of Medicine, Houston, TX
2Department of Neuro-oncology, The Brain Tumor Center, University of Texas M.D. Anderson Cancer Center, Houston, TX

Introduction

Immunotherapy has been established as standard treatment for multiple malignancies, including melanoma, renal cell carcinoma, Hodgkin lymphoma, and non-small cell lung cancer. A specific form of immunotherapy involves immune checkpoint blockade of cytotoxic T-lymphocyte antigen 4 (CTLA-4) or programmed death-1 (PD-1) ligand PD-L1, thereby “taking the brakes off” the immune system. Immune-mediated complications of multiple organ systems have been described, including the skin, GI tract, kidney, PNS, liver, lymph, and hematopoietic system. The literature, however, does not contain many cases of neurologic complications related to the use of immuno-therapy. Here we present a series of patients who were treated with several checkpoint inhibitors and developed multiple neurologic complications, including myasthenia gravis (MG), Guillain Barre syndrome (GBS), and myositis.

Case 1

A 70-year-old female with metastatic melanoma treated with ipilimumab for the past month presented to the ER after an episode of syncope. She has had a progressive decline in physical function and endurance. A week prior to presentation she began experiencing orthostatic hypotension, sinus tachycardia, drenching sweats, dry eyes, and urinary frequency.

Nerve conduction studies demonstrated normal to mildly prolonged distal latencies in the upper and lower extremities, with borderline normal to reduced amplitudes. Sensory studies were normal. Repetitive nerve stimulation at 2-Hz revealed an approximate 10% decrement at 10% of the stimulation duration.

Examination was notable for truncal ataxia, neck flexion weakness, bilateral foot drop, and ataxia on toe lift, with no fasciculation. Lumbar puncture showed elevated protein (79), elevated WBC (13), and normal glucose and RBC count.

Clinical exam was notable for restricted up-gaze, bilateral facial weakness, dysarthria, neck extension weakness, and fatigability of bilateral deltoid muscles. Electromyography (EMG) showed 12% decrement with 2-Hz repetitive stimulation of the left accessory nerve and left facial nerve, concerning for myasthenia gravis. EMG was also notable for myopathic features, including U-shaped curve. Nerve conduction studies demonstrated a decrement of 12% at 1-minute post-exercise, with a U-shaped curve. A similar response was recorded in the right ulnar nerve, with a decrement of 12% at 1-minute post-exercise.

The patient was treated with five sessions of plasma exchange with minimal improvement. This was followed with IVIG for five days, with repeat infusions every two for a total of three courses over six weeks, and finally was given a steroid taper with significant improvement in strength, speech, and swallowing ability.

Conclusions

• Musculoskeletal toxicities are more probable with PD-1 and PD-L1 inhibitors compared to CTLA-4.

References

2. Yi Q, Pirskanen R, Lefvert AK. Human muscle acetylcholine receptor reactive T and B lymphocytes in the peripheral blood of patients with myasthenia gravis. Brain. 1999;122(Pt 8):1681-1688.