Neurologic complications in cancer patients exposed to checkpoint inhibitors

Michael N. Youssef[1], Rebecca A. Harrison[2], Karin Woodman[2], Merry Chen[2]

[1]Department of Neurology, Baylor College of Medicine, Houston, TX

[2]Department 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), programmed cell death 1 (PD–1) or its ligand PD-L1, thereby "taking the brakes off" the immune system. Immune-mediated complications of multiple organ systems have been associated with this treatment, including the skin, GI tract, kidney, PNS, liver, lymph node, eye, pancreas, and the endocrine 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.

Exam was notable for truncal and appendicular ataxia, 4/5 strength throughout, and reduced ankle reflexes (1+). EMG revealed a moderate, generalized, sensorimotor polyneuropathy with both axonal and demyelinating features meeting criteria for GBS.

Lumbar puncture showed elevated protein (79), elevated WBC (13), and normal glucose and RBC count. Cytology revealed reactive lymphocytes with no malignant cells. She received daily IVIG for five days with notable improvement in strength and orthostatic lightheaded-ness. This was followed by a 5-day prednisone taper.

At follow-up one month after discharge, the only notable symptom was orthostatic hypotension.

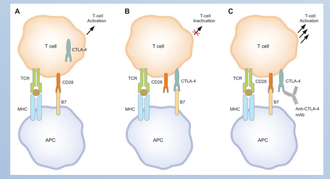
Case 2

A 67-year-old male with squamous cell carcinoma of the left parotid gland with metastasis to the lung and bone, currently on treatment with nivolumab, presented for evaluation of difficulty arising from a seated position and climbing stairs. Seven months after completing therapy, he developed lung metastases, and was initiated on nivolumab therapy at 3mg/kg every two weeks for disease progression.

One week after the third dose of nivolumab, he noted difficulty rising from chair and climbing stairs. The following week, he was admitted to the hospital for evaluation of progressive proximal muscle weakness. Initial laboratory evaluation demonstrated an elevated creatine kinase of >2800 and elevated transaminase levels (AST 141, ALT 162). He was hydrated and sent home.

One week later he returned with dysphagia, ptosis, and shortness of breath. Examination was notable for bilateral ptosis, bilateral restricted eye abduction, dysconjugate eye movements on sustained up-gaze, and bifacial weakness. He had generalized fatigable weakness of his extremities graded 4/5 diffusely and worst in deltoids and hip flexors which were 4-/5; neck flexors and extensors were 4/5. His abnormal transaminase and creatine kinase levels were resolving. His arterial blood gas reflected hypercarbic respiratory failure with a pCO2 of 72 on arterial blood gas. As such, he was admitted to the intensive care unit for non-invasive ventilation and observation.

Action of CTLA-4 inhibitors



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 of the right accessory nerve revealed 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 maximum 6% decrement. His vital capacity improved from 1.3 prior to drug therapy to 2.1 liters within minutes after receiving physostigmine 1 mg. Concentric needle electromyography of select muscles in the upper and lower extremities revealed mild ongoing denervation and early recruitment of myopathic motor units. Serologic evaluation revealed negative acetylcholine receptor antibodies; however, the paraneoplastic panel returned positive for striated muscle autoantibody. CT chest was negative for thymoma.

After EMG confirmed the diagnosis of myasthenia, he was treated with intravenous immunoglobulin (IVIG) for five days, with resulting improvement in dyspnea. He was able to be weaned from the BIPAP to supplemental oxygen. He was transitioned to oral prednisone 80 mg daily and discharged to a rehabilitation facility. His presentation was attributed to the nivolumab, leading to its discontinuation.

Case 3

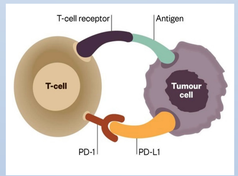
A 65-year-old woman with a history of leiomyosarcoma, diagnosed in September 2012 and treated with neoadjuvant chemotherapy and limb sparing right axillary dissection in June 2013; she had disease recurrence in the left lower lung treated with wedge resection in December 2015 and new left pleural lesions treated with durvalumab and tremelimumab. She presented with back pain, stooped posture with difficulty lifting her head, and progressive weakness in the proximal upper and lower extremities after beginning durvalumab and tremelimumab.

Concurrently, her urine became brown in color and she was increasingly having shortness of breath, difficulty swallowing, droopy eyes, facial weakness, and decreased volume of her voice.

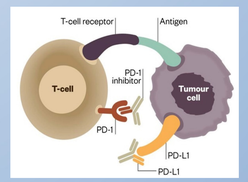
Clinical exam was notable for restricted up-gaze, bilateral facial weakness, dysarthria, neck extension weakness, and fatigability of bilateral deltoid muscles. Electromyography (EMG) showed 12% decrement with 2-Hz repetitive stimulation of the left accessory nerve and left facial nerve, concerning for myasthenia gravis. EMG was also notable for myopathic features including irritable findings in the tibialis anterior and gastrocnemius, along with mildly reduced recruitment.

Labs obtained include a CK on admission of 19,794 and positive acetylcholine binding, blocking, and modulating antibodies. A paraneoplastic panel was checked and returned positive for anti-striated muscle antibody.

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 weeks 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.



Action of PD-1 and PD-L1 inhibitors



Case 4

An 81-year-old female with urachal cancer currently off treatment (last chemotherapy two months prior to arrival was atezolizumab, a PD-L1 inhibitor) presented for evaluation of head drop, left facial droop, voice changes, dysarthria, and proximal weakness. She was previously hospitalized for about three weeks after her NSTEMI when symptoms developed and was then transferred for respiratory weakness. She was intubated and transferred to intensive care unit.

Exam on BiPAP was notable for ability to follow simple commands, left ptosis, left facial asymmetry, dysarthria, neck extensor strength of 3/5 and neck flexor strength of 4/5. Arm strength bilaterally was 3/5 proximally and 4/5 distally, and leg strength was 4/5 proximally and 5/5 distally. Reflexes were 1+ in the arms, absent in the legs, and plantar reflexes were flexor.

EMG revealed a moderate, generalized myopathic process with irritable features and moderate, generalized, axonal sensorimotor polyneuropathy. Repetitive stimulation of spinal accessory muscles was notable for a decremental change.

Labs were negative for neuromuscular junction transmission disorders, including Acetylcholine receptor binding, blocking, and modulating antibodies, P/Q and the N-type calcium channel antibodies, and anti-striated muscle antibody. CK was 554.

She required intubation. She started plasma exchange for five cycles, and given minimal improvement was given an infusion of rituximab. She was also started on mycophenolate and pulse dose steroids; however, she continued to decline. Respiratory status remained poor and her family elected for comfort measures only.

Conclusions

- Musculoskeletal toxicities are more probable with PD-L1 and PD-1 inhibitors compared to CTLA-4 inhibitors.
- When patients are treated with dual immune check-point inhibitors, neuromuscular complications were reported more frequently and with increased severity.
- Current management guidelines call for use of corticosteroids for treatment of severe complications, and intravenous immunoglobulin and plasma exchange.
- In cases of severe neurologic toxic effect, checkpoint inhibitors are permanently discontinued.
- The patients presented exhibited classic symptoms consistent with their conditions: myasthenia gravis, Guillain-Barre syndrome, and myositis. While under-reported in the literature, neurologic complications are important to identify and treat without delay, given that the presentation of neurologic conditions may be classical or atypical, and multiple conditions may present simultaneously. Due to the increasing use of immunotherapies in oncology, increased recognition, characterization, and understanding of the neurologic complications of these therapies is essential amongst clinicians so that rapid workup and treatment may occur.

References

1. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: A systematic review of case reports. PloS One. 2016;11:e0160221.
2. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378:158-168.
3. Supakonnumporn S, Katirji B. Guillain-Barre syndrome triggered by immune checkpoint inhibitors: A case report and literature review. J Clin Neuromuscul Dis. 2017;19:80-83.
4. Chen JH, Lee KY, Hu CJ, Chung CC. Coexisting myasthenia gravis, myositis, and polyneuropathy induced by ipilimumab and nivolumab in a patient with non-small-cell lung cancer: A case report and literature review. Medicine (Baltimore). 2017;96:e9262.
5. Sieb JP. Myasthenia gravis: An update for the clinician. Clin Exp Immunol. 2014;175:408-418.
6. Yi Q, Piriaknen R, Lefvert AK. Human muscle acetylcholine receptor reactive T and B lymphocytes in the peripheral blood of patients with myasthenia gravis. J Neuroimmunol. 1993;42:215-222.
7. Vincent A, Rothwell P. Myasthenia gravis. Autoimmunity 2004;37:317-319.
8. Kimura T, Fukushima S, Miyashita A, et al. Myasthenic crisis and polymyositis induced by one dose of nivolumab. Cancer Sci. 2016;107:1055-1058.
9. Loochtan AI, Nickoloff MS, Hobson-Webb LD. Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer. Muscle Nerve. 2015;52:307-308.
10. Polat P, Donofrio PD. Myasthenia gravis induced by nivolumab therapy in a patient with non-small-cell lung cancer. Muscle Nerve. 2016;54:507.
11. Imafuku K, Yoshino K, Ymaguchi K, Tsuboi S, Ohara K, Hata H. Nivolumab therapy before vemurafenib administration induces a severe skin rash. J Eur Acad Dermatol Venereol. 2017 Mar;31(3):e169-e171.
12. Tanaka R, Fujisawa Y, Maruyama H, et al. Nivolumab-induced thyroid dysfunction. Jpn J Clin Oncol. 2016;46:575-579.
13. Sciacca G, Nicoletti A, Rampello L, Noto L, Parra HJ, Zappia M. Benign form of myasthenia gravis after nivolumab treatment. Muscle Nerve. 2016;54:507-509.
14. Shiraz T, Sano T, Kamijo F, et al. Acetylcholine receptor binding antibody-associated myasthenia gravis and rhabdomyolysis induced by nivolumab in a patient with melanoma. Jpn J Clin Oncol. 2016;46:86-88.
15. Carrera W, Baartman BJ, Kosmorsky G. A case report of drug-induced myopathy involving extraocular muscles after combination therapy with tremelimumab and durvalumab for non-small cell lung cancer. Neuroophthalmology. 2017;41:140-143.
16. Abdel-Rahman O, Elsobgy M, Oweira H, Giryes A, Tekbas A, Decker M. Immune-related musculoskeletal toxicities among cancer patients treated with immune checkpoint inhibitors: A systematic review. Immunotherapy. 2017;9:1175-1183.
17. Fellner A, Makrava C, Lotem M, et al. Neurologic complications of immune checkpoint inhibitors. J Neurooncol. 2018.
18. Hottinger AF. Neurologic complications of immune checkpoint inhibitors. Curr Opin Neurol. 2016;29:806-812.
19. Images: https://www.pharmaceutical-journal.com/news-and-analysis/features/immune-checkpoint-inhibitors-bring-new-hope-to-cancer-patients/20067127.article, https://www.sciencedirect.com/science/article/pii/S1556086415332196

Download poster