Nivolumab-induced immune-mediated neurotoxicity in Hodgkin lymphoma

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ABSTRACT

Nivolumab, a monoclonal antibody against programmed cell death-1 used to treat multiple cancers, has fewer side effects than traditional chemotherapy but has displayed a propensity to cause a host of immune-related adverse events. We describe a case of nivolumab immune-mediated neurotoxicity in a 42-year-old Hispanic man with relapsed Hodgkin lymphoma who presented with unilateral facial droop, dysarthria, and dysphagia 1 week after receiving nivolumab. His symptoms rapidly improved with steroids, intravenous immunoglobulin, and infliximab.

KEYWORDS Hodgkin lymphoma; immune-mediated adverse reaction; neurotoxicity; nivolumab

Checkpoint inhibitors are a new class of immunotherapy drugs targeting immune system checkpoints such as the programmed cell death-1 (PD-1) receptor of T cells, preventing receptor binding to programmed death ligand-1 (PD-L1) of tumor cells and allowing T cell activation and tumor cell death. These drugs can cause unique side effects related to nonspecific immune system activation, also termed immune-related adverse events (irAEs).¹ We present the case of a 42-year-old man with relapsed classical Hodgkin lymphoma who developed facial droop, dysarthria, and dysphagia 1 week after receiving the checkpoint inhibitor nivolumab.

CASE PRESENTATION

A 42-year-old man with recently relapsed classical Hodgkin lymphoma presented to the emergency department with sudden-onset headache, right-sided facial droop, dysarthria, and dysphagia. He previously developed dysphagia after receiving pembrolizumab (Keytruda). His first dose of nivolumab (Opdivo) was 1 week prior to presentation. He developed diffuse body aches 2 days afterwards and the presenting neurological symptoms 7 days afterwards. On examination, his blood pressure was 136/88 mm Hg; heart rate, 87 beats per minute; respiratory rate, 18 breaths per minute; and temperature, 97.6°F. He had right-sided lagophthalmos, right facial droop with upper and lower right-sided facial weakness, and 3/5 bilateral lower-extremity motor weakness. His cardiopulmonary and abdominal exam was unremarkable.

His white blood cell count was $23.7 \times 10^3/\mu\text{L}$ (92.6% neutrophils). A noncontrast computed tomography scan of the head revealed no abnormalities. Cerebrospinal fluid (CSF) analysis revealed an elevated white blood cell count of 37 cells/ μL (normal, 0–5 cells/ μL), with 87% lymphocytes, 12% monocytes, and 1% macrophages; a red blood cell count of 2 cells/ μL ; glucose of 71 mg/dL; and protein of 141 mg/dL. CSF Gram stain, culture, and polymerase chain reaction testing were negative for any infectious etiology. Flow cytometry on the CSF identified no abnormal cell populations, and the paraneoplastic antibody panel was unremarkable. Magnetic resonance imaging (MRI) revealed bulging of the L4-L5 and L5-S1 discs with mild to moderate neural foraminal compromise (*Figures 1–3*).

The patient was diagnosed with nivolumab-induced immune-mediated central nervous system toxicity. He received high-dose intravenous methylprednisolone (2 g daily) for 5 days followed by two doses of infliximab (10 mg/kg weekly $\times$ 2 doses) and intravenous immunoglobulin (IVIG; 30 g daily for 5 days) for persistent neurological deficits. Over the next 2.5 weeks, his dysphagia and lower-limb weakness gradually improved, and he was discharged on a 4-week oral prednisone taper. Six months after discharge, the dysphagia and other neurological deficits had resolved. Nivolumab was discontinued permanently due to his grade 4 neurotoxicity.

DISCUSSION

Immune checkpoint inhibitors have proven effective in treating various cancers. They work by blocking checkpoint

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Figure 1. Sagittal MRI images. (a) Precontrast T1 non-fat-saturated image demonstrates the hypointense lumbar spinal cord and sacral nerve roots (white arrows). (b, c) Postcontrast T1 fat-saturated image demonstrates subtle enhancement (black arrows) of the spinal cord and sacral nerve roots.

Figure 2. Axial MRI images. (a) Precontrast T1 non-fat-saturated image demonstrates the hypointense sacral nerve roots (white arrows). (b) Postcontrast T1 fat-saturated image demonstrates subtle enhancement (black arrows) of the sacral nerve roots and denervation-related abnormal muscle enhancement in the paraspinal/back muscles (white arrows).

pathway receptors on cytotoxic T cells normally co-opted by cancer cells to evade cytotoxic T-cell-mediated death via activation of the apoptosis pathway.² T cells and B cells are upregulated and proliferated by immunotherapy. During the proliferative phase, autoreactive T and B cells can go unchecked and cause unpredictable autoimmune side effects.³ The pathogenesis of these side effects is unclear. It has been postulated that multifocal, small-vessel vasculopathy and disruption of the blood-nerve barrier may play a role.⁴ Previous studies have shown a strong correlation between the response rate and irAEs, and irAEs are more common in patients receiving a combination of multiple checkpoint inhibitors when compared to either drug alone, such as in the treatment of melanoma.^{5–7} A review of 59 clinical trials showed that the incidence of neurological side effects was 6.1% when receiving anti-PD-1 antibodies; however, most side effects were limited to mild headache and peripheral sensory neuropathy, and only 1% were more severe.⁸ More severe presentations encompass a broad spectrum of neurological syndromes

Figure 3. Sagittal postcontrast T1 non-fat-saturated MRI image demonstrates subtle enhancement (white arrows) of the medulla and cervical spinal cord.

including myasthenia gravis, aseptic meningitis, encephalitis, Guillain Barre–like syndromes, transverse myelitis, and posterior reversible encephalopathy syndrome.^{8,9}

Management of side effects relies on early symptom recognition and ruling out other causes of neurological decline, such as cancer progression, seizure, infection, or metabolic derangements. Symptoms are graded from mild (grade 1, no functional impairment) to severe (grade 4, limiting self-care); for mild symptoms, the checkpoint inhibitor can be continued under close observation. For grade 2 symptoms (those that interfere with some activity), therapy can be held and corticosteroids can be considered. Higher grades of toxicity may require pulse-dose corticosteroids in addition to IVIG and plasmapheresis.¹⁰ IVIG and plasmapheresis initiated within 2 weeks of onset of symptoms has been shown to improve recovery time.^{11,12} Infliximab, a chimeric monoclonal antibody against tumor necrosis factor- α , may be useful in treating severe steroid/IVIG-refractory symptoms as in our patient; however, its role in the treatment of neurologic irAE is unknown, and current guidelines do not recommend it for neurotoxicity.^{13–15}

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1. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5:95. doi:10.1186/s40425-017-0300-z.

2. Dine J, Gordon R, Shames Y, et al. Immune checkpoint inhibitors: an innovation in immunotherapy for the treatment and management of patients with cancer. *Asia Pac J Oncol Nurs*. 2017;4:127–135. doi: [10.4103/apjon.apjon_4_17](https://doi.org/10.4103/apjon.apjon_4_17).
3. Postow M, Wolchok J. Toxicities associated with checkpoint inhibitor immunotherapy. In: Atkins MB, ed. *UpToDate*. Waltham, MA: UpToDate; 2017.
4. Manousakis G, Koch J, Sommerville RB, et al. Multifocal radiculoneuropathy during ipilimumab treatment of melanoma. *Muscle Nerve*. 2013;48:440–444. doi: [10.1002/mus.23830](https://doi.org/10.1002/mus.23830).
5. Attia P, Phan GQ, Maker AV, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. *J Clin Oncol*. 2005;23:6043–6053. doi: [10.1200/JCO.2005.06.205](https://doi.org/10.1200/JCO.2005.06.205).
6. Downey SG, Klapper JA, Smith FO, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. *Clin Cancer Res*. 2007;13(Pt 1):6681–6688. doi: [10.1158/1078-0432.CCR-07-0187](https://doi.org/10.1158/1078-0432.CCR-07-0187).
7. Garcia CA, El-Ali A, Rath TJ, et al. Neurologic immune-related adverse events associated with adjuvant ipilimumab: report of two cases. *J Immunother Cancer*. 2018;6:83. doi: [10.1186/s40425-018-0393-z](https://doi.org/10.1186/s40425-018-0393-z).
8. Cuzzubbo S, Tissier M. P04.08: neurological adverse events associated with immune checkpoint inhibitors: review of the literature and characterization of the neurological patterns. *Neuro Oncol*. 2016;18(Suppl 4):iv25–iv26. doi: [10.1093/neuonc/now188.086](https://doi.org/10.1093/neuonc/now188.086).
9. Williams TJ, Benavides DR, Patrice KA, et al. Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. *JAMA Neurol*. 2016;73:928–933. doi: [10.1001/jamaneurol.2016.1399](https://doi.org/10.1001/jamaneurol.2016.1399).
10. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36:1714–1768. doi: [10.1200/JCO.2017.77.6385](https://doi.org/10.1200/JCO.2017.77.6385).
11. Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2014;(9):CD002063. doi: [10.1002/14651858.CD002063.pub6](https://doi.org/10.1002/14651858.CD002063.pub6).
12. Raphaël JC, Chevret S, Hughes RAC, et al. Plasma exchange for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2012;(7):CD001798. doi: [10.1002/14651858.CD001798.pub2](https://doi.org/10.1002/14651858.CD001798.pub2).
13. Thaipisuttikul I, Chapman P, Avila EK. Peripheral neuropathy associated with ipilimumab: a report of 2 cases. *J Immunother*. 2015;38:77–79. doi: [10.1097/CJI.0000000000000070](https://doi.org/10.1097/CJI.0000000000000070).
14. Abdallah AO, Herlopian A, Ravilla R, et al. Ipilimumab-induced necrotic myelopathy in a patient with metastatic melanoma: a case report and review of literature. *J Oncol Pharm Pract*. 2016;22:537–542. doi: [10.1177/1078155215572932](https://doi.org/10.1177/1078155215572932).
15. Stenger M. ASCO clinical practice guideline: management of immune-related adverse events from immune checkpoint inhibitor therapy. *The ASCO Post*. May 25, 2018. <https://www.ascopost.com/issues/may-25-2018/asco-clinical-practice-guideline-immune-related-adverse-events/>.