Immunotherapy Induced Myasthenic-Like Syndrome in a Metastatic Melanoma Patient With Amyotrophic Lateral Sclerosis

Clinical Medicine Insights: Oncology
Volume 14: 1–3

DOI: 10.1177/1179554920978024
SAGE

Muhammad Jaffer[1], Matthew Chung[1,2], Esha Sharda[1], Asha Ramsakal[1,3], Edwin Peguero[1,3], Neha Verma[1,3] and Sepideh Mokhtari[1,3]

[1]University of South Florida, Tampa, FL, USA. [2]MD Anderson Cancer Center, Houston, TX, USA. [3]Moffitt Cancer Center, Tampa, FL, USA.

ABSTRACT: Immunotherapy agents such as ipilimumab and nivolumab are immensely effective in the treatment of various malignancies. Despite this, neurologic immune-related sequelae (NIRS) have been observed. Prompt diagnosis and treatment is critical to improve patient outcomes. We present a case of a 63-year-old man with stage IV metastatic melanoma beginning treatment with ipilimumab and nivolumab. Gathered history from the patient showed that he had a 3-year presentation of bradykinesia, shuffling gait, and muscle cramping. After one dose, the patient began to have progressively worsening generalized weakness; after receiving the immunotherapy, there was a rapid decline in his health. In addition to weakness, the patient developed diplopia, impaired single breath count, lingual and upper/lower extremity fasciculations, and brisk reflexes. While the lumbar puncture and myasthenia panel were non-diagnostic, the electromyography (EMG) revealed axonal neuropathy and diffuse denervation/reinnervation changes. Furthermore, a magnetic resonance imaging (MRI) displayed fatty replacement of the tongue with a bright tongue sign. These results pointed to the diagnosis of amyotrophic lateral sclerosis (ALS) superimposed onto myasthenic-like syndrome. The patient was started on various treatments; however, unfortunately he died due to acute hypoxic respiratory failure. This case highlights important considerations that must be taken when using immunotherapy, especially in patients with pre-existing neurological deficits. Furthermore, it shows the importance of early diagnosis as treatment can potentially cure adverse sequelae.

KEYWORDS: anti-PD-1, anti-CTLA4, checkpoint inhibitor, immunotherapy, melanoma, metastatic brain tumors, toxicity management, combination immunotherapy, adverse event management

RECEIVED: May 2, 2020. **ACCEPTED:** November 9, 2020.

TYPE: Case Report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Muhammad Jaffer, University of South Florida, 4202 E Fowler Ave, Tampa, FL 33620, USA. Email: mjaffer@usf.edu

Immune checkpoint inhibitors (ICIs) have gained prominence in the treatment of a wide variety of cancers. Concomitant with their therapeutic potential, several neurologic immune-related sequelae (NIRS) have been identified.[1]

Observation

A 63-year-old man with stage IV (BRAF negative) metastatic melanoma presented with progressively worsening generalized weakness after a single dose of ipilimumab and nivolumab. Prior to having received immunotherapy, he had reported 3-year gradual onset of bradykinesia, shuffling gait, muscle cramping, and foot drop. He had seen a neurologist after being diagnosed with metastatic melanoma 6 months prior and was receiving dopaminergic treatment under the surmise of paraneoplastic Parkinsonism. After immunotherapy (which was promptly discontinued thereafter), his weakness dramatically worsened, requiring multiple hospital admissions. On examination, he was noted to have upward gaze diplopia, impaired single breath count, and lower motor neuron symptoms such as lingual and upper and lower extremity fasciculations, atrophy (interosseous, deltoid, and quadriceps muscles), and tongue fibrillations. He also had upper motor neuron findings such as 3+ deep tendon reflexes with positive palmomental, bilateral crossed adductor, and Hoffman reflexes. Creatine kinase levels were normal and lumbar puncture with paraneoplastic panel was unrevealing; an extended myositis panel, myasthenic panel (acetylcholine receptor modulating, blocking, and binding antibodies), and voltage-gated calcium channel antibodies were non-diagnostic.

Table 1. Results of electromyography.

NAME	INSERTIONAL ACTIVITY	FIBRILLATIONS	POSITIVE SHARP WAVES	POLYPHASIA	FASCICULATIONS	RECRUITMENT
L. Tibialis Ant	Increased	2+	1+	Increased	++	Decreased
L. Gastroc. Med	Normal	2+	1+	Increased	++	Decreased
L. Biceps Brach	Normal	2+	1+	Increased	++	Decreased
L. Deltoid	Increased	3+	1+	Increased	++	Decreased

Nonetheless, patient demonstrated significant clinical improvement after high-dose steroids, maintaining on pyridostigmine 30 mg every 8 hours and prednisone 50 mg twice a day only to worsen after steroid tapering. An electromyography (EMG) revealed evidence of a widespread neuropathic process with diffuse denervation and re-innervation (see Table 1); furthermore, a magnetic resonance imaging (MRI) displayed fatty replacement of the tongue with a bright tongue sign (Figure 1), raising suspicion for amyotrophic lateral sclerosis (ALS). He was treated with IV methylprednisolone 250 mg/day and IV immunoglobulin at 1 gm/kg over 2 days followed by 5 cycles of plasmapheresis 1 week later due to high suspicion for superimposed myasthenic-like syndrome, but unfortunately died from acute hypoxic respiratory failure.

Discussion

Prior literature has reported exacerbations of underlying multiple sclerosis[2] and myasthenia gravis[3] in the context of ICI administration. However, this represents the first case of its kind where a patient with suspected underlying ALS developed worsening neurological deficits post-ICI administration.

A key point in this case was the fact that initial diagnosis of ALS was confounded by generalized systemic weakness in the context of known melanoma, as well as the surmised diagnosis of paraneoplastic Parkinsonism. However, after ICI administration, while the patient also suffered from a concomitant myasthenic-like syndrome that was responsive to steroids and pyridostigmine, clinical findings suggestive of ALS also emerged more dramatically (Figure 2). Whether this was attributable to the natural temporal progression of ALS or an immunomodulatory effect remains unclear.

While use of ICIs has been cautioned against in presence of known autoimmune diseases due to potential precipitation of flare-ups,[4,5] such caveats have not heretofore been expressed for ALS, given its neuroinflammatory status has been contentious in the literature thus far.[6] This case report suggests caution is prudent in suspected ALS cases, with careful evaluation of ICI risks before initiation.

The case report suggests pre-existing neurological deficits, including ALS, could be risk factors for NIRS, and more specific neurological screening may serve to risk-stratify patients prior to treatment with ICIs. Further research regarding the

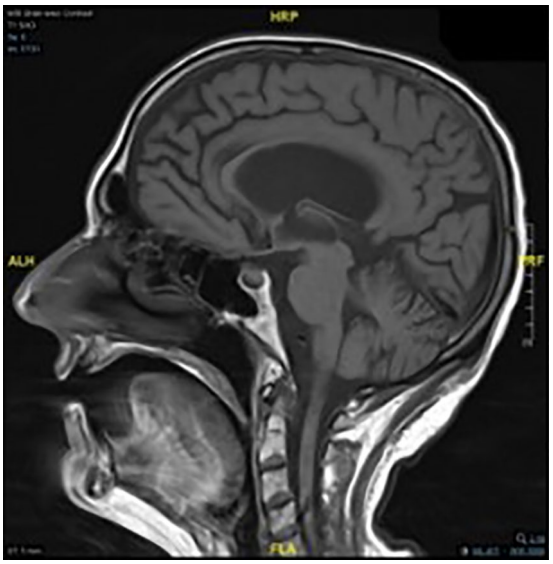

Figure 1. Bright tongue sign.

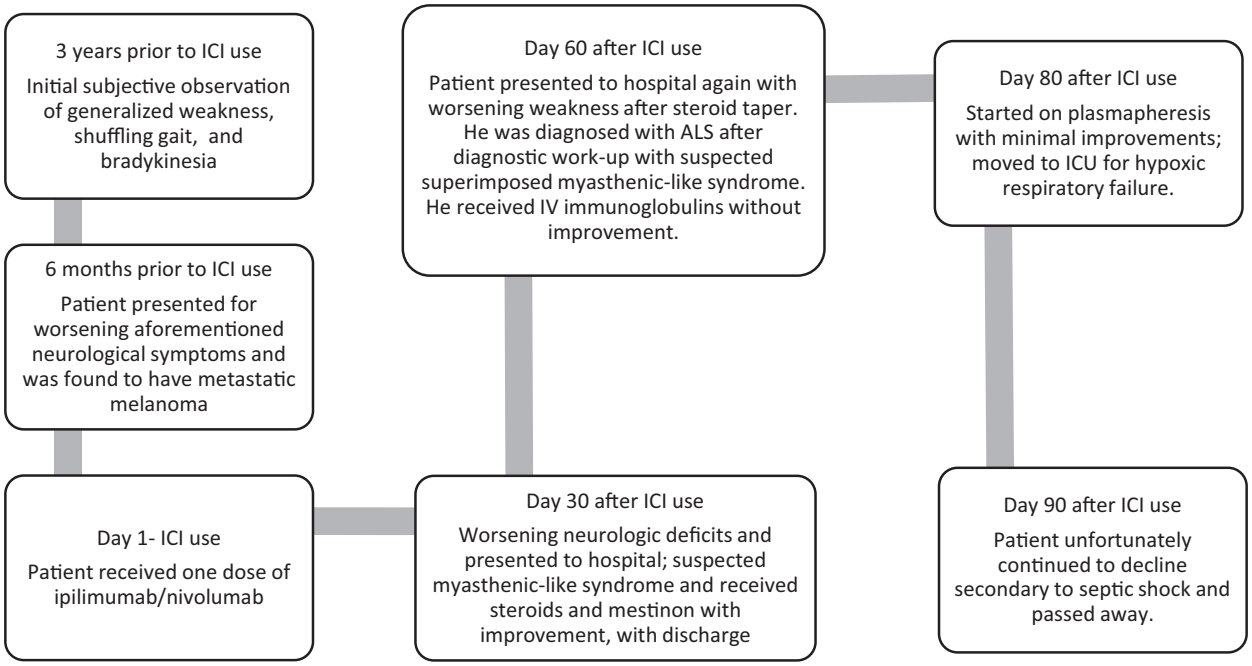

Figure 2. Timeline of events (milestones are presented without regard to timescale). ALA indicates amyotrophic lateral sclerosis; ICI, Immune checkpoint inhibitor.

safety of ICI use in patients with underlying neurological deficits may guide future therapeutic decision-making.

Acknowledgements

The authors thank Dr Karl Kasischke for his help in reviewing and providing feedback on the manuscript.

Author Contributions

MJ was the primary writer of this manuscript. SM and NV shared as co-senior authors. All authors read and approved the final manuscript.

Consent for Publication

The patient's legal representative provided posthumous consent for publication of the patient information and images included in this manuscript.

ORCID iD

Muhammad Jaffer https://orcid.org/0000-0002-4218-2346

REFERENCES

1. 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 guidelines. *J Clin Oncol* 2018;36:1714-1768.
2. Gettings EJ, Hackett CT, Scott TF. Severe relapse in a multiple sclerosis patient associated with ipilimumab treatment of melanoma. *Mult Scler* 2014;21:670-670.
3. Cooper DS, et al. Severe exacerbation of myasthenia gravis associated with checkpoint inhibitor immunotherapy. *J Neuromuscul Dis* 2017;4:169-173.
4. Dalakas MC. Neurological complications of immune checkpoint inhibitors: what happens when you "take the brakes off" the immune system. *Ther Adv Neurol Disord* 2018;11:1-9.
5. Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders (AD) or major toxicity with ipilimumab (IPI). *J Clin Oncol* 2016;34:9515-9515.
6. Lyon MS, Wosiski-Kuhn M, Gillespie R, Caress J, Milligan C. Inflammation, immunity, and amyotrophic lateral sclerosis: I. Etiology and pathology. *Muscle Nerve* 2018;59:10-22.