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, and 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 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

**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.

| NAME            | INSERTATIONAL ACTIVITY | FIBRILLATIONS | POSITIVE SHARP WAVES | POLYPHASIA | FASCICULATIONS | RECRUITMENT |
|-----------------|------------------------|---------------|----------------------|------------|----------------|-------------|
| L. Tibialis Ant | Increased              | 2+            | 1+                   | Increased  | ++             | Decreased   |
| L. Gastrocn.    | Normal                 | 2+            | 1+                   | Increased  | ++             | Decreased   |
| L. Biceps Brach | Normal                 | 2+            | 1+                   | Increased  | ++             | Decreased   |
| L. Deltoid Brach| Increased              | 3+            | 1+                   | Increased  | ++             | Decreased   |

Table 1. Results of electromyography.
Nonetheless, patient demonstrated significant clinical improvement after high-dose steroids, maintaining on pyridostigmine 30mg every 8 hours and prednisone 50mg 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 and myasthenia gravis 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, such caveats have not heretofore been expressed for ALS, given its neuroinflammatory status has been contentious in the literature thus far. 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...
safety of ICI use in patients with underlying neurological deficits may guide future therapeutic decision-making.

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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.

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