Clinical Case Reports International

Case Report
Published: 10 Aug, 2023

# Myasthenia Gravis as an Adverse Effect of Immune Checkpoint Inhibitors: A Case Report

*Rivera VS, Núñez Pérez IJ and Brenes NJ**

*University of Costa Rica, Costa Rica*

## Abstract

Immune Checkpoint Inhibitors (ICI) are valuable therapeutic agents that enable targeted oncological treatment by interfering with key evasion mechanisms used by cancer cells. However, this therapy, by inducing a T-cell-mediated immune response disinhibition, can potentially trigger a cascade of immune toxicity with a wide range of manifestations affecting multiple systems. Myasthenia Gravis (MG) as an adverse effect of immune checkpoint inhibitors has a reported incidence of approximately 0.24%. Despite its low incidence, when it occurs as an immune-mediated adverse effect, it carries a high mortality rate, emphasizing the importance of the early recognition of its manifestations. We present a case of a 68-year-old male who developed *de novo* myasthenic syndrome as a secondary adverse effect of anti-PD-L1 therapy, specifically Atezolizumab.

**Keywords: Immune checkpoint inhibitors; PD-1; PD-L1; CTLA-4; Atezolizumab; Myasthenia gravis**

## Introduction

Cancer cells employ inhibitory signals on T-cells as a mechanism to evade detection and elimination by the immune system. Immune Checkpoint Inhibitors (ICI) function by suppressing the inactivation signals on T-cells [1,2]. Once the inhibitory signal is removed, an enhanced immune response is triggered, leading to the elimination of abnormal cells [3].

However, this heightened immune response can also unleash an unpredictable cascade of autoimmune toxicity known as Immune-related Adverse Events (IrAEs). IrAEs have been reported with a frequency of 60% to 90% for CTLA-4 inhibitors and 20% to 70% for PD-1/PD-L1 inhibitors, with the majority being grade 1 to 2 events [1,3,4].

IrAEs typically occur within 3 to 6 months after treatment initiation and commonly affect systems with high cellular turnover, such as the skin, endocrine, gastrointestinal, renal, and pulmonary systems. However, neurological involvement, as described in the case presented below, has also been observed, albeit much less frequently [3-6].

Various ICIs, based on their target molecules, include Cytotoxic T-lymphocyte-Associated protein 4 (CTLA-4) inhibitors (e.g., ipilimumab, tremelimumab), programmed cell Death Protein 1 (PD-1) inhibitors (e.g., nivolumab, pembrolizumab, cemiplimab), and programmed cell Death-Ligand 1 (PD-L1) inhibitors (e.g., atezolizumab, avelumab, durvalumab). Additionally, the inhibitor targeting Lymphocyte Activation Gene 3 (LAG-3: relatlimab) has recently been added to the group.

## Case Presentation

We present the case of a 68-year-old male with a history of well-controlled type 2 diabetes mellitus, dyslipidemia, and hypertension. In June 2020, he was diagnosed with unresectable multifocal trabecular hepatocellular carcinoma secondary to Non-Alcoholic Steatohepatitis (NASH) with Child-Pugh A classification.

In October 2020, the patient started treatment with the combination of atezolizumab and bevacizumab, approved for systemic treatment of advanced hepatocellular carcinoma. Regular evaluations during the first 7 months of treatment showed significant improvement in liver function tests and alpha-fetoprotein levels (normalizing from 300 ng/ml to within the normal range), along with substantial clinical and functional improvement and Computed Tomography (CT) imaging indicating a partial response according to RECIST criteria. However, in April 2021 (6 months into treatment), he presented to the hospital emergency department with a 4-day history of progressive generalized weakness, necessitating the use of a wheelchair for mobility. He also

OPEN ACCESS

***Correspondence:***
*Natalia Jiménez Brenes, Musculoskeletal Tumors, University of Costa Rica, Costa Rica*

**Received Date**: *20 Jul 2023*
**Accepted Date:** *04 Aug 2023*
**Published Date:** *10 Aug 2023*

***Citation:***
*Rivera VS, Núñez Pérez IJ, Brenes NJ. Myasthenia Gravis as an Adverse Effect of Immune Checkpoint Inhibitors: A Case Report. Clin Case Rep Int. 2023; 7: 1592.*

COMMENTS: 213511887

| Test Name | In Range | Out of Range | Reference Range |
|---|---|---|---|
| Acetylcholine Rec Binding | | | |
| **Acetylcholine Rec Bind Ab** | | **4.90 H** | nmol/L |
| | Reference Ranges for Acetylcholine Receptor Binding Antibody: | | |
| | Negative: < or =0.30 nmol/L<br>Equivocal: 0.31-0.49 nmol/L<br>Positive: > or =0.50 nmol/L | | |
| ACETYLCHOLINE RECEPTOR | | | |
| Acetylcholine Rec Bloc Ab | <15 | | <15 % Inhibition |
| ACETYLCHOLINE RECEPTOR | | | |
| **Acetylcholine Rec Mod Ab** | | **81 H** | % Inhibition<br><32% INHIBITION |

**Figure 1:** Measurement of anti-acetylcholine receptor antibodies.

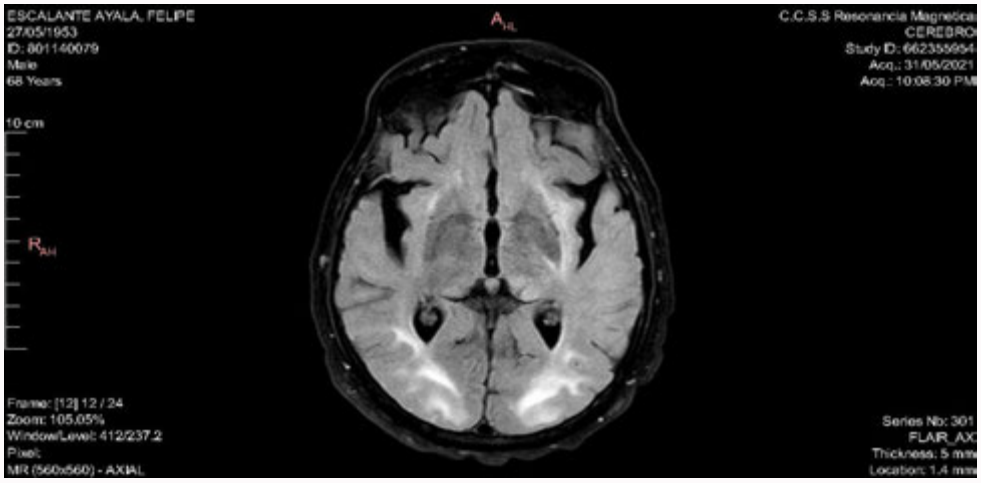


**Figure 2:** Brain MRI showing findings of Posterior Reversible Leukoencephalopathy Syndrome (PRES).

exhibited bilateral ptosis worsening throughout the day, weakness in neck flexion, difficulty swallowing, dyspnea, shallow breathing, and fatigue, with preserved level of consciousness. During hospitalization the patient experienced respiratory decompensation, requiring acute management with endotracheal intubation and invasive mechanical ventilation. CT imaging of the chest and abdomen and AFP levels at that time indicated disease control.

Due to the suggestive clinical presentation of myasthenic syndrome, measurements of Anti-Acetylcholine Receptor Antibodies (Figure 1) were obtained, confirming the diagnosis of myasthenic syndrome. The patient was admitted to the Intensive Care Unit (ICU), where Intravenous Immunoglobulin G (IVIg), neostigmine, corticosteroids, azathioprine and plasmapheresis were administered.

During his ICU stay, the patient experienced *de novo* seizures. CT and Magnetic Resonance Imaging (MRI) of the Central Nervous System (CNS) ruled out brain metastases. The MRI showed symmetrical white matter edema in the parieto-occipital and cerebellar regions, consistent with Posterior Reversible Encephalopathy Syndrome (PRES) (Figure 2). Cerebrospinal fluid analysis revealed acellular fluid with normal glucose levels and elevated protein levels with negative culture and autoimmune encephalitis antibodies.

Eventually, the patient was extubated and gradually recovered from myasthenic syndrome and PRES symptoms, continuing neurological treatment on an outpatient basis.

Due to the association between myasthenic syndrome and ICI use, atezolizumab was discontinued, and subsequent treatment with bevacizumab monotherapy was initiated. However, after 7 months of monotherapy, the patient experienced disease progression and eventually passed away.

Neurological IrAEs that affect the CNS include conditions such as hypophysitis, aseptic meningitis, non-infectious encephalitis or myelitis, diffuse encephalopathy, rheumatological CNS diseases, and Posterior Reversible Encephalopathy Syndrome (PRES). Meanwhile, myositis, Myasthenia Gravis (MG), Guillain-Barré Syndrome (GBS), and other polyneuropathies fall under the category of Peripheral Nervous System (PNS) involvement [3,7].

## Discussion

Neurological immune-related Adverse Events (N-irAEs) have an incidence of about 1% to 6% [3,5,7]. N-irAEs can be divided into two major groups: those affecting the Central Nervous System (CNS) and those affecting the Peripheral Nervous System (PNS). Within the CNS group, conditions such as hypophysitis, aseptic meningitis, non-infectious encephalitis or myelitis, diffuse encephalopathy, rheumatological CNS diseases, and Posterior Reversible Encephalopathy Syndrome (PRES) have been described. The PNS group includes myositis, Myasthenia Gravis (MG), Guillain-Barré Syndrome (GBS), and other polyneuropathies [3,7]. Among drug-induced MG cases, ICI therapy appears to be the most common cause,

with an incidence reported in small studies of approximately 0.24% [8]. Notably, Nivolumab (anti-PD-1) use has been associated with an incidence of ICI-induced MG as high as 0.12% [9]. Myasthenic syndrome typically occurs within the first 3 months after treatment initiation, either *de novo* (due to ICI use) or as an exacerbation of pre-existing disease [1,10]. According to available data, the majority of cases (85%) present *de novo* syndrome induced by ICIs, while a smaller number manifest as exacerbations, predominantly associated with anti-PD-1 use [11].

Clinical manifestations include ocular weakness and fatigability (ptosis, diplopia), bulbar weakness (dysphagia, dyspnea), and weakness in proximal muscles. ICI-induced MG may concur with varying degrees of myopathy in 37% to 51% of cases and myocardial involvement in 8% to 16% of cases [1,6,8,10].

Diagnostic approaches may include serological tests for acetylcholine receptor or anti-Musk antibodies, Tensilon or ice pack test, electromyography with repetitive nerve stimulation, CT or MRI, CSF analysis, and nerve sample biopsy [5,11]. Importantly, some patients may present with seronegative myasthenic syndrome induced by ICIs, with a seropositivity rate of 59% [10]. Management involves discontinuation of the ICI and the use of drugs such as neostigmine, immunosuppressants, corticosteroids, rituximab, mycophenolate, IVIg, or plasmapheresis in case of clinical deterioration, as was the case with our patient [1,5,6,12].

Although most patients have a favorable outcome, mortality rates range from 20% to 30%, with respiratory failure being the most frequent cause. Therefore, assessing potential indicators of respiratory failure is crucial [1,3,10].

## Conclusion

Immune checkpoint inhibitors have ushered in a new era in the treatment of various types of cancer, with expanding therapeutic indications. However, these novel medications have distinct toxicological profiles and pose a vulnerability of the CNS and PNS, making their use challenging.

ICI-induced MG, along with other N-irAEs, is a rare but potentially lethal complication associated with multiple daily life impairments. It has a high severity rate and often co-occurs with other autoimmune conditions, such as myositis and myocardial involvement. It also exhibits a distinct serological profile, necessitating clinical tests and electromyography to confirm the diagnosis.

Early diagnosis, discontinuation of the triggering agent, early recognition of risk factors for respiratory deterioration, and symptomatic management with anticholinesterases, immunosuppressants, and respiratory therapy form the basis of its management.

## References


1. Santomasso BD. Anticancer drugs and the nervous system. Continuum. 2020;26(3):732-64.
2. De Mello RA, Veloso AF, Esrom Catarina P, Nadine S, Antoniou G. Potential role of immunotherapy in advanced non-small-cell lung cancer. Onco Targets Ther. 2017;10:21-30.
3. Yoo MJ, Long B, Brady WJ, Holian A, Sudhir A, Gottlieb M. Immune checkpoint inhibitors: An emergency medicine focused review. Am J Emerg Med. 2021;50:335-44.
4. Wang SJ, Dougan SK, Dougan M. Immune mechanisms of toxicity from checkpoint inhibitors. Trends Cancer. 2023;9(7):543-53.
5. Perrinjaquet C, Desbaillets N, Hobnger AF. Neurotoxicity associated with cancer immunotherapy: Immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy. Curr Opin Neurol. 2019;32(3):500-510.
6. Ho AK, Ho AM-H, Cooksley T, Nguyen G, Erb J, Mizubu GB. Immune-related adverse events associated with immune checkpoint inhibitor therapy. Anesth Analg. 2021;132(2):374-83.
7. Winter SF, Vaios EJ, Dietrich J. Central nervous system injury from novel cancer immunotherapies. Curr Opin Neurol. 2020;33(6):723-35.
8. Safa H, Johnson DH, Trinh VA, Rodgers TE, Lin H, Suarez-Almazor ME, et al. Immune checkpoint inhibitor related myasthenia gravis: Single center experience and systemic review of the literature. J Immunother Cancer. 2019;7(1):319.
9. Suzuki S, Ishikawa N, Konoeda F, Seki N, Fukushima S, Takahashi K, et al. Nivolumabrelated myasthenia gravis with myosis and myocarditis in Japan. Neurology [Internet]. 2017;89(11):1127-34.
10. Marini A, Bernardini A, Gigli GL, Valente M, Muñiz-Castrillo S, Honnorat J, et al. Neurologic adverse events of immune checkpoint inhibitors. Neurology. 2021;96(16):754-66.
11. Rodolico C, Nicocia G, Damato V, Antonini G, Liguori R, Evoli A. Benefit and danger from immunotherapy in myasthenia gravis. Neurol Sci. 2021;42(4):1367-75.
12. Sullivan RJ, Weber JS. Immune-related toxicities of checkpoint inhibitors: Mechanisms and mitigation strategies. Nat Rev Drug Discov. 2021;21(7):495-508.