

Pembrolizumab-Induced Myasthenia Gravis and Myositis: Literature Review on Neurological Toxicities of Programmed Death Protein 1 Inhibitors

Alfred Schwab^a, Marc Assaad^{b, c}, Rachelle Hamadi^b, Juda Zurndorfer^a,
Racha Abi Melhem^b, Jennifer Holtzbach^a, Jeffrey Loeffler^b,
Muhammad Ibrahim^a

Abstract

We present herein the case of an elderly male patient, who was receiving immunotherapy for his urothelial cancer and who presented to our facility with lower extremity weakness. The patient was diagnosed with myasthenia gravis, thyroiditis, myositis and myocarditis, which were considered as immune adverse events of pembrolizumab therapy. The patient received pyridostigmine, intravenous immunoglobulin, plasmapheresis, corticosteroids, and rituximab with mild improvement of his symptoms. The patient had some neurological recovery, was discharged to a nursing facility, however he was ventilator dependent. Of importance, our case is followed by review and discussion of the literature related to immunotherapy and its side effects.

Keywords: Pembrolizumab; Monoclonal antibody; Immunotherapy; Myasthenia gravis; Neurotoxicity; Monoclonal antibody; Immune checkpoint inhibitor; Immune-related adverse events

Introduction

Pembrolizumab (Keytruda) is a monoclonal antibody that targets programmed death protein 1 (PD-1) and is considered an immune checkpoint inhibitor (ICI). It is widely used in many solid organ tumors including but not limited to non-small cell lung carcinoma, urothelial carcinoma, renal cell carcinoma and melanoma [1]. PD-1 is expressed on activated T lymphocytes that links usually to programmed death ligand 1 (PDL-

1), which is excessively expressed by tumoral cells in order to evade the immune system. Pembrolizumab blocks this interaction by blocking PD-1 receptor, thus activating the immune system against malignant cells [2, 3]. The inhibition of the immune checkpoint PD-1/PDL-1 results in upregulation or enhancement of cytotoxic T lymphocyte activity against cancer [1]. This is how Keytruda, along with other immunotherapeutic agents, has changed the course of metastatic diseases and has shown favorable results in advanced stages of the illness [4].

However, there is the risk of activated T lymphocytes attacking normal tissue and leading to autoimmune toxicity [4]. Immunotherapy is very well known to cause immune-related adverse events (irAEs) that are very well described, staged, and managed by many oncological societies [5]. Severity of the irAEs is graded from 1 to 5 from mild symptoms to death respectively. Manifestations of autoimmune reactions vary from mild, such as skin rashes to severe, including Steven-Johnson syndrome with mucosal involvement. Patients often present with diarrhea, hypo- or hyperthyroidism, hypopituitarism, adrenal failure and pneumonitis [1, 2, 5, 6]. These autoimmune syndromes or irAEs are usually dose-dependent [5] and cease with early diagnosis and discontinuation of the offending agent. Neurological toxicities, while rare, occurring in 5% of patients receiving PD-1 inhibitor, can cause rapid clinical deterioration and be potentially fatal [4, 7, 8]. Furthermore, the incidence of such severe irAEs (grade 3) in patients is upwards of 15% [4, 5].

In the following case, we present a known but rare complication of pembrolizumab in a patient with bladder neoplasia who presents with immune-mediated myositis, myocarditis, thyroiditis, and myasthenia gravis (MG) with bulbar involvement leading to respiratory failure and invasive ventilation.

Case Report

Investigations

This is a case of an 81-year-old male with a past medical history of hypertension, hypothyroidism, benign prostatic hyperplasia, and an extensive smoking history of 65 pack-

Manuscript submitted September 13, 2022, accepted November 8, 2022
Published online xx xx, 2022

^aDivision of Neurocritical Care, Department of Neurology, Staten Island University Hospital, Staten Island, NY 10305, USA

^bDepartment of Medicine, Staten Island University Hospital, Staten Island, NY 10305, USA

^cCorresponding Author: Marc Assaad, Department of Medicine, Staten Island University Hospital, Staten Island, NY 10305, USA.
Email: massaad@northwell.edu

doi: <https://doi.org/10.14740/jmc4008>

year, presenting to our facility for evaluation of progressive bilateral lower extremity weakness and pain. The patient had been diagnosed the previous year with stage III bladder cancer and underwent a cystectomy and subsequently treated with adjuvant immunotherapy with pembrolizumab every 3 weeks, and have completed two cycles. In the emergency department, the patient's vital signs were stable, and his neurological exam was remarkable for decreased motor strength in bilateral lower extremities, graded as 3/5. The laboratory workup was evident for a creatine phosphokinase (CPK) of 6,500 U/L, elevated troponin level initially at 1.43 ng/mL, mild transaminitis, and acute kidney injury with a creatinine of 1.7 mg/dL. The patient was admitted for treatment of rhabdomyolysis. The patient did not exhibit any cardiac symptomatology, his electrocardiogram (EKG) findings were not suggestive of acute coronary syndrome, and as such, medical management was recommended by the cardiology team. Patient's lower extremity weakness did not improve which has prompted the neurology evaluation for concern of myositis and empiric prednisone was initiated. A non-contrast computed tomography (CT) of the brain was obtained which displayed an old right thalamic infarct, and the magnetic resonance imaging (MRI) of the cervical and lumbar spine revealed degenerative changes, without evidence of cord compression. However, the MRI did show diffuse paraspinal soft tissue edema reflective of myositis. Along with these findings, MRI of bilateral lower extremities revealed diffuse edema in the right adductor, rectus femoris, vastus medialis, vastus intermedius and vastus lateralis muscles. Additional milder degree of muscle edema was noted in the greater saphenous and semitendinosus. Findings were suggestive of myositis. Cardiac enzymes kept increasing before stabilizing, rising the suspicion of myocarditis. Transthoracic echocardiogram (TTE) did not show any wall motion abnormality and estimated left ventricular ejection fraction (LVEF) was > 60%. Thyroid-stimulating hormone was 28.25 μ IU/mL along with low free thyroxine level of 0.6 ng/dL. Further laboratory results are detailed in Table 1.

Diagnosis

Within 2 weeks of his hospitalization, the patient developed dysphagia, diplopia, and a significant left eyelid droop, minimally responsive to the ice pack test, along with bilateral upper extremity weakness. As the patient's respiratory status deteriorated, he was intubated for impending respiratory failure and upgraded to the neurocritical care unit for treatment of MG crisis. At that time, the patient's negative inspiratory force (NIF) was -18 cmH₂O, and his vital capacity was 850 mL. CT of the chest failed to reveal any thymoma. The MG serological workup was all negative including acetylcholine receptor (AChR) antibody, muscle-specific kinase (MuSK) antibody, lipoprotein receptor-related protein 4 (LRP4) antibody, and voltage-gated calcium channel (VGCC) antibody (Table 1). Furthermore, the patients' myo-marker and paraneoplastic marker were negative as well. Nerve conduction studies revealed low motor amplitude suggestive of a neuromuscular

junction (NMJ) disorder as shown in Figure 1. The pathology of his left thigh muscular biopsy revealed severe acute myonecrosis suggestive of an immune-mediated process. Patient was diagnosed with pembrolizumab-induced MG (iMG), myositis with concomitant myocarditis and thyroiditis.

Treatment

Treatment with pyridostigmine 60 mg three times daily and high-dose intravenous methylprednisolone of 1 g daily was initiated. Despite corticosteroids, the neurological status of the patient did not improve, prompting the initiation of intravenous immunoglobulin (IVIG). The patient was also receiving thyroid replacement therapy with higher dose of levothyroxine 150 μ g daily. After the failure of the above-mentioned therapy, patient underwent plasmapheresis at day 6 from intensive care unit admission. Due to his inability to wean from the ventilator and prolonged intubation, tracheostomy, and a percutaneous endoscopic gastrostomy (PEG) were performed. One gram infusion of rituximab (anti-CD20) was initiated, and intravenous methylprednisolone was switched to 1 mg/kg of prednisone orally and slowly tapered over the next 4 weeks.

Follow-up and outcomes

After 4 weeks of hospitalization, the patient's neurological symptoms started to improve and the patient was able to move bilateral lower extremities, but he did not regain his baseline motor function. The patient was discharged to a nursing facility after achieving medical stability.

Discussion

To summarize, our 81-year-old male patient was receiving Keytruda treatment for bladder neoplasia. Within 2 months of initiation of therapy, patient presented to the hospital complaining of lower extremity weakness which worsened during the hospital course and was accompanied with new onset myasthenia like syndrome that manifested as ptosis, diplopia, and dysphagia. The patient has required invasive ventilation because of his respiratory failure. Patient was diagnosed with pembrolizumab autoimmune syndrome that includes MG, myositis, thyroiditis, and myocarditis. Patient was treated with IVIG, plasmapheresis, high-dose steroid, pyridostigmine and rituximab. Towards the end of his hospital course, his motor power improved but still was ventilator-dependent via a tracheostomy.

As mentioned previously, neurotoxicity from PD-1 inhibitors is rare; however, there are many reported neurological complications including encephalitis, meningitis, cranial neuropathy, multiple sclerosis, Guillain-Barre syndrome, MG and transverse myelitis [4, 8, 9]. These complications may affect both the central and the peripheral nervous system [10, 11] and appear within 3 months of therapy initiation [12]. Clinical presentations include but are not limited to change in mental

Table 1. Laboratory Findings

Laboratory test	Day 1	Day 4	Day 9	Day 16
CK, U/L	6,500	9,244	5,841	1,115
Troponin, ng/mL	1.43	1.72	4.4	3.56
CK-MB, ng/mL	153	207	31.3	29.8
Pro-BNP, pg/mL	8,205			
TSH, μ IU/mL	28.25			
FT4, ng/dL	0.6			
ESR, mm/h	89			
CRP, mg/L	117			
VGCC Ab, pmol/L	0.0			
Anti-Jo-1 Ab, U	< 20			
Anti-U3 RNP	Negative			
Anti-U2 snRNP	Negative			
Anti-U1 RNP, U	< 20			
PL-7 PL-12	Negative			
EJ OJ	Negative			
SRP	Negative			
MI-2	Negative			
TIF-gamma P155/140	Negative			
MDA-5 (P140), U	< 20			
NXP-2, U	< 20			
Anti-PM/Scl-100, U	< 20			
Ku	Negative			
Anti-SSA IgG, U	< 20			
AchR Ab	14%			
Ach modulating Ab	0%			
P/Q type Ab, nmol/L	0.01			
LRP4 Ab	Negative			
MuSK Ab, U/mL	< 1			
AMA	< 1:20			
Microsomal antibody assay	< 20.1			
SMA	< 1:20			
ANA	Negative			

Ab: antibody; Ach: acetylcholine; AchR: acetylcholine receptor; AMA: antimitochondrial antibody; ANA: antinuclear antibody; CK: creatine kinase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FT4: free thyroxine; IgG: immunoglobulin G; LRP4: low-density lipoprotein receptor-related protein 4; MuSK: muscle-specific kinase; PM: polymyositis; Pro- BNP: brain natriuretic peptide; RNP: ribonucleoprotein; SMA: smooth muscle antibody; SRP: signal recognition particle; SSA: Sjogren syndrome-related antigen A; TSH: thyroid-stimulating hormone; VGCC: voltage-gated calcium channel.

status, seizure, weakness and focal deficit [4]. Reynolds et al have listed a screening tool for each of ICI-mediated neurotoxicity along with appropriate treatment based on irAEs grade [12]. The incidence of MG as a consequence of PD-1 antagonist initiation is 30-37% according to a case series analysis [1]. Further literature review revealed that there have been similar presentations to our patient's clinical course including those with bladder cancer who developed myositis, MG and myo-

carditis [7, 13-18]. The evidence highlights the possibility of certain relation between the type of malignancy and the organ or system affected by ICI, especially since iMG has been associated with concurrent myocarditis and myositis in 8% in similar cases [4, 19].

The median time of iMG onset from starting ICI is usually 1 month and the most common presenting symptom is ptosis [19]. In our case, MG autoantibodies (AchR and MuSK anti-

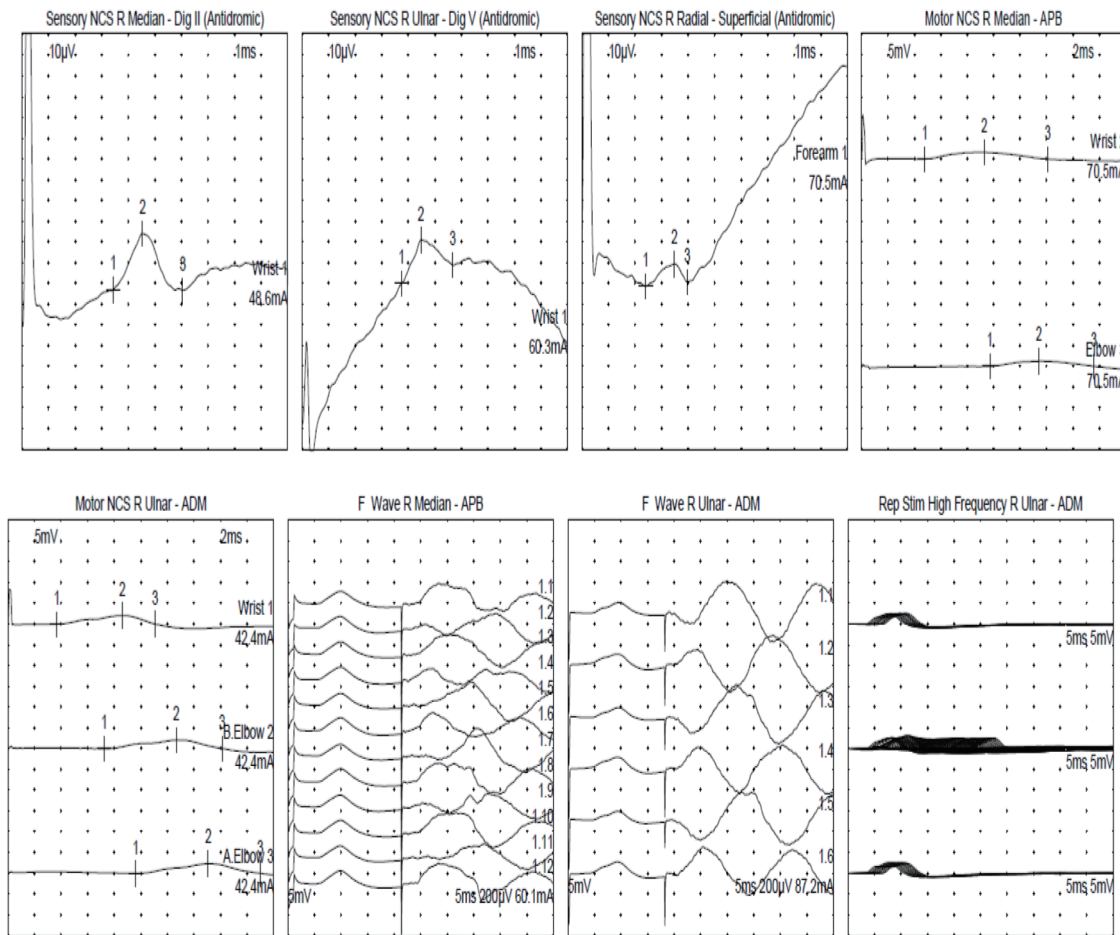


Figure 1. Nerve conduction study. F: frequency; ms: millisecond; mV: millivolt; NCS: nerve conduction study; R: right; Rep: repetitive; Stim: stimulation.

bodies) were negative as well as the paraneoplastic workup and the antinuclear antibody (ANA) were all negative. While AchR antibodies are often negative in ICI-mediated MG, and the diagnosis made clinically, there have been cases with positive serological markers [4, 11-13]. An association between similar reactions and human leukocyte antigen (HLA) A02, HLA-B08 and HLA-DRB1*03 is described [15] which might be a helpful screening tool before the initiation of ICI.

The ICI-mediated MG often presents with bulbar involvement leading to respiratory failure within 1 week requiring invasive ventilation in up to 50% of patients [4, 19]. Those with elevated CPK tend to develop respiratory compromise more than those without rhabdomyolysis according to Safa et al [19]. The complete resolution of iMG symptoms and deficits is uncommon and as such, the sequelae of the disease process persist [1, 4]. Cruz et al found that the mortality rate of ICI-mediated MG is 30% [7].

Early diagnosis of neurotoxicity and iMG is crucial for the improvement of clinical outcome because the discontinuation of the immunotherapy is the important initial step [1]. In iMG as in MG, recommended therapeutic regimens include plasmapheresis, IVIG, high-dose steroids for acute symptomatic

disease, as well as pyridostigmine which also has a clinical benefit [1]. Many experts suggest that high-dose methylprednisolone (1 g) is the first line agent and plasmapheresis is indicated when corticotherapy fails [1, 13]. Such doses are needed to overcome to the blood-brain barrier and to achieve better central nervous system penetration [1]. Other experts report a better outcome with the initiation of IVIG and plasmapheresis regardless of MG severity and prefer these modalities over steroids and other agents because the latter need time to achieve immunosuppression [19]. In our case, rituximab was used as a steroid tapering agent and it is also recommended by Cruz et al for a patient with a similar condition [7]. The use of other agents is also reported such as anti-tumor necrosis factor alpha (TNF- α) and cyclosporin [1]. The discontinuation of ICI in severe adverse events is recommended, and future use or resumption of these agents should be cautiously monitored. If the grade of severity of irAEs is below or equal to 3, and autoimmune symptoms have quickly resolved, it is possible to resume same ICI regimen [12].

Despite the deleterious effect of ICI, it is well known that the development of irAEs is indicative of therapeutic response. Survivors among patients with iMG or neurotoxicity related to

irAEs had favorable outcome and higher tumor responsiveness [1, 19].

We describe in our case, a rare but severe complication of immunotherapy. Oncologists and internists should be aware of these manifestations to stop the medication as soon as possible, which remains the major key for recovery. Different immunosuppressive modalities are used to treat the auto-immune process; however, neurotoxicity can be fatal or irreversible.

Learning points

Neurological toxicity from PD-1 inhibitor, such as MG, is rare, however can be fatal and can have long-term sequelae. MG caused by pembrolizumab, might be irreversible and has a high mortality rate. Autoimmune antibodies in this case may be negative and the diagnosis remains clinical. Early discontinuation of the culprit medication and early treatment with immunosuppressants are the key to improving prognosis. Plasmapheresis and IVIG are preferred over immunosuppressive treatment earlier in the disease course. Rituximab is a drug to consider in patients with pembrolizumab-induced MG and might have a potential benefit in other immune-mediated neurological complications.

Acknowledgments

We would like to thank the Internal Medicine Research Department and the Department of Neurology, Division of Neuro-Critical Care at Staten Island University Hospital for helping us finalize the project.

Financial Disclosure

This paper received no financial support from any third party.

Conflict of Interest

The authors declare that there is no conflict of interest.

Informed Consent

Informed consent has been obtained.

Author Contributions

All authors have made contributions to writing this case report. Marc Assaad, Rachelle Hamadi, Juda Zurndorfer, Racha Abi Melhem, Jeffrey Loeffler and Jennifer Holtzbach helped drafting the manuscript. Juda Zurndorfer and Jennifer Holtzbach participated in data collection. Alfred Schwab and Muhammad Ibrahim are responsible for the concept, editing and supervision.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

- Feng S, Coward J, McCaffrey E, Coucher J, Kalokerinos P, O'Byrne K. Pembrolizumab-induced encephalopathy: a review of neurological toxicities with immune checkpoint inhibitors. *J Thorac Oncol.* 2017;12(11):1626-1635.
- Sonpavde GP, Grivas P, Lin Y, Hennessy D, Hunt JD. Immune-related adverse events with PD-1 versus PD-L1 inhibitors: a meta-analysis of 8730 patients from clinical trials. *Future Oncol.* 2021;17(19):2545-2558.
- Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). *Hum Vaccin Immunother.* 2016;12(11):2777-2789.
- Haugh AM, Probasco JC, Johnson DB. Neurologic complications of immune checkpoint inhibitors. *Expert Opin Drug Saf.* 2020;19(4):479-488.
- Darnell EP, Mooradian MJ, Baruch EN, Yilmaz M, Reynolds KL. Immune-Related Adverse Events (irAEs): diagnosis, management, and clinical pearls. *Curr Oncol Rep.* 2020;22(4):39.
- Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, Schmidgen MI, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer.* 2016;60:190-209.
- Crusz SM, Radunovic A, Shepherd S, Shah S, Newey V, Phillips M, Lim L, et al. Rituximab in the treatment of pembrolizumab-induced myasthenia gravis. *Eur J Cancer.* 2018;102:49-51.
- Gonzalez NL, Puwanant A, Lu A, Marks SM, Zivkovic SA. Myasthenia triggered by immune checkpoint inhibitors: New case and literature review. *Neuromuscul Disord.* 2017;27(3):266-268.
- Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugurel S, Thomas I, Schmidgen MI, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer.* 2016;60:210-225.
- Mohn N, Beutel G, Gutzmer R, Ivanyi P, Satzger I, Skripuletz T. Neurological immune related adverse events associated with nivolumab, ipilimumab, and pembrolizumab therapy-review of the literature and future outlook. *J Clin Med.* 2019;8(11):1-15.
- Liewluck T, Kao JC, Mauermann ML. PD-1 Inhibitor-associated Myopathies: Emerging Immune-mediated Myopathies. *J Immunother.* 2018;41(4):208-211.
- Reynolds KL, Guidon AC. Diagnosis and management of immune checkpoint inhibitor-associated neurologic toxicity: illustrative case and review of the literature. *Oncologist.* 2019;24(4):435-443.
- Takai M, Kato D, Iinuma K, Maekawa YM, Nakane K, Tsuchiya T, Yokoi S, et al. Simultaneous pembrolizumab-induced myasthenia gravis and myocarditis in a patient with metastatic bladder cancer: A case report. *Urol Case*

- Rep. 2020;31:101145.
14. Hayakawa N, Kikuchi E, Suzuki S, Oya M. Myasthenia gravis with myositis induced by pembrolizumab therapy in a patient with metastatic urothelial carcinoma. *Int Cancer Conf J*. 2020;9(3):123-126.
 15. Botta C, Agostino RM, Dattola V, Cianci V, Calandrucchio ND, Bianco G, Mafodda A, et al. Myositis/myasthenia after pembrolizumab in a bladder cancer patient with an autoimmunity-associated HLA: immune-biological evaluation and case report. *Int J Mol Sci*. 2021;22(12):1-8.
 16. Todo M, Kaneko G, Shirotake S, Shimada Y, Nakano S, Okabe T, Ishikawa S, et al. Pembrolizumab-induced myasthenia gravis with myositis and presumable myocarditis in a patient with bladder cancer. *IJU Case Rep*. 2020;3(1):17-20.
 17. Tian CY, Ou YH, Chang SL, Lin CM. Pembrolizumab-induced myasthenia gravis-like disorder, ocular myositis, and hepatitis: a case report. *J Med Case Rep*. 2021;15(1):244.
 18. Alnahhas I, Wong J. A case of new-onset antibody-positive myasthenia gravis in a patient treated with pembrolizumab for melanoma. *Muscle Nerve*. 2017;55(6):E25-E26.
 19. Safa H, Johnson DH, Trinh VA, Rodgers TE, Lin H, Suarez-Almazor ME, Fa'ak F, et al. Immune checkpoint inhibitor related myasthenia gravis: single center experience and systematic review of the literature. *J Immunother Cancer*. 2019;7(1):319.