Journal of Community Hospital Internal Medicine Perspectives

Volume 14 | Issue 3 Article 17

2024

Pembrolizumab-induced Myasthenia Gravis and Myocarditis

Jisun Won
Abington Memorial Hospital, Department of Internal Medicine, USA, jyw164@jefferson.edu

Edward Zhao
Abington Memorial Hospital, Department of Internal Medicine, USA

Melissa States
Abington Memorial Hospital, Department of Internal Medicine, USA

Rachel Brown
Abington Memorial Hospital, Department of Internal Medicine, USA

Abdallah El-habr
Abington Memorial Hospital, Department of Internal Medicine, USA

See next page for additional authors

Recommended Citation

Won, Jisun; Zhao, Edward; States, Melissa; Brown, Rachel; El-habr, Abdallah; and Damsker, Jason (2024) "Pembrolizumab-induced Myasthenia Gravis and Myocarditis," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 14: Iss. 3, Article 17.
DOI: 10.55729/2000-9666.1352
Available at: https://scholarlycommons.gbmc.org/jchimp/vol14/iss3/17

Pembrolizumab-induced Myasthenia Gravis and Myocarditis

Authors

Jisun Won, Edward Zhao, Melissa States, Rachel Brown, Abdallah El-habr, and Jason Damsker

Pembrolizumab-induced Myasthenia Gravis and Myocarditis

Jisun Won*, Edward Zhao, Melissa States, Rachel Brown, Abdallah El-habr, Jason Damsker

Abington Memorial Hospital, Department of Internal Medicine, USA

Abstract

As the use of immune checkpoint inhibitors (ICPi) such as pembrolizumab is rapidly expanding in the field of immuno-oncology, it is crucial for healthcare providers to be aware of their immune-related adverse events (irAE) which are thought to be driven by augmented immune response of T-cells. While neurologic irAE are underrepresented in literature, their consequences could lead to fatal outcomes. In this report, we describe the case of a patient with excellent performance status prior to pembrolizumab therapy who subsequently suffered myasthenic crisis eventually requiring tracheostomy and long-term mechanical ventilation.

Keywords: Pembrolizumab, Myasthenia gravis, Immune checkpoint inhibitors, Immune-related adverse events

1. Introduction

Immune checkpoint inhibitors (ICPi) have been rapidly expanding their use across multiple types of cancers and have revolutionized the field of immuno-oncology. Despite their benefit in cancer therapy, their immunomodulatory properties have led to the emergence of side effects termed immune-related adverse events (irAE).[1] Below, we present a case of a patient who presented with profound respiratory weakness secondary to pembrolizumab-induced myasthenia gravis (MG) requiring long-term mechanical ventilation.

2. Case presentation

A 75-year-old male with a past medical history of urothelial carcinoma came to the hospital with complaints of shortness of breath and chest pressure associated with generalized weakness. His oncologic history was significant for high-grade urothelial carcinoma of the bladder with muscle invasion. He underwent transurethral resection of the bladder tumor, but a follow-up computed tomography (CT) urogram demonstrated a recurrent tumor. After a detailed discussion of risks and benefits, the patient was started on pembrolizumab and received his second dose approximately a month before the hospital presentation. In addition, the patient was previously known to have a right bundle branch block (RBBB) and had received pharmacologic stress test two years prior which was negative for ischemia. During that time, he had also received transthoracic echocardiogram (TTE) which revealed 60% left ventricular ejection fraction (LVEF), moderate left ventricular hypertrophy, grade 1 diastolic dysfunction and mild to moderate aortic regurgitation.

On admission, initial bloodwork was significant for elevated troponin of 1480 ng/L with electrocardiogram (ECG) redemonstrating RBBB and bifascicular block but otherwise nonspecific ST segment changes. Due to the elevated troponin, the patient underwent coronary angiography which only revealed mild coronary artery disease not requiring any intervention. Nonetheless, troponins continued to rise to a peak of 3111 ng/L and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels also increased to 1952 pg/mL. TTE revealed normal left ventricular size and function with no pericardial effusion.

Received 11 December 2023; revised 28 February 2024; accepted 25 March 2024.
Available online 7 May 2024

* Corresponding author.
E-mail address: jisun.won@jefferson.edu (J. Won).

https://doi.org/10.55729/2000-9666.1352

Meanwhile, the patient experienced progressively worsening shortness of breath and weakness with no active disease seen on chest or head imaging. Over time, our patient experienced hypercapnic respiratory failure accompanied by dysphagia, decreased cough reflexes, and mucous plugging requiring intubation. Serology workup revealed positive acetylcholine receptor (AchR) antibodies with significantly elevated titers of 2.94 nmol/L (reference range: positive ≥0.50 nmol/L). At this stage, providers raised concerns for pembrolizumab-induced MG, and treatment consisting of intravenous immunoglobulin (IVIG) (0.4/kg/dose), intravenous methylprednisolone (1 g/day), and pyridostigmine (120 mg/day) was initiated. However, the patient's respiratory functions failed to improve after finishing 5 days of IVIG therapy and subsequent treatment with plasmapheresis led to minimal success. Adjunctive treatment with rituximab was discontinued after two doses due to the development of infectious complications. Eventually, the patient received tracheostomy for long-term ventilation needs and was discharged to a skilled nursing facility.

3. Discussion

Pembrolizumab is a monoclonal antibody against programmed death receptor 1 (PD-1).[2] PD-1 can bind to programmed cell death protein 1 ligand 1 (PD-L1) which can further bind to CD80-activated T-cells leading to cellular inhibition. Certain tumor cells express PD-L1 and utilize this inhibitory property to evade immune attack from the host. Thus, pembrolizumab inhibits the binding of the ligand to the receptor, enabling T-cells to recognize and attack tumor cells.

While the use of anti-PD-1/PD-L1 antibodies has been rapidly expanding, studies have revealed a range of irAE resulting from the augmented immune response driven by T-cell activation (see Fig. 1). While neurologic and cardiac irAE are less commonly seen, they are associated with a high mortality rate.[1] The severity of irAEs can be rated from grade 1 through grade 4 using the Common Terminology Criteria for Adverse Events grading system (CTCAE). The adverse events are categorized by organ systems such as pulmonary, dermatologic, neurologic, cardiac, et cetera.[13] In

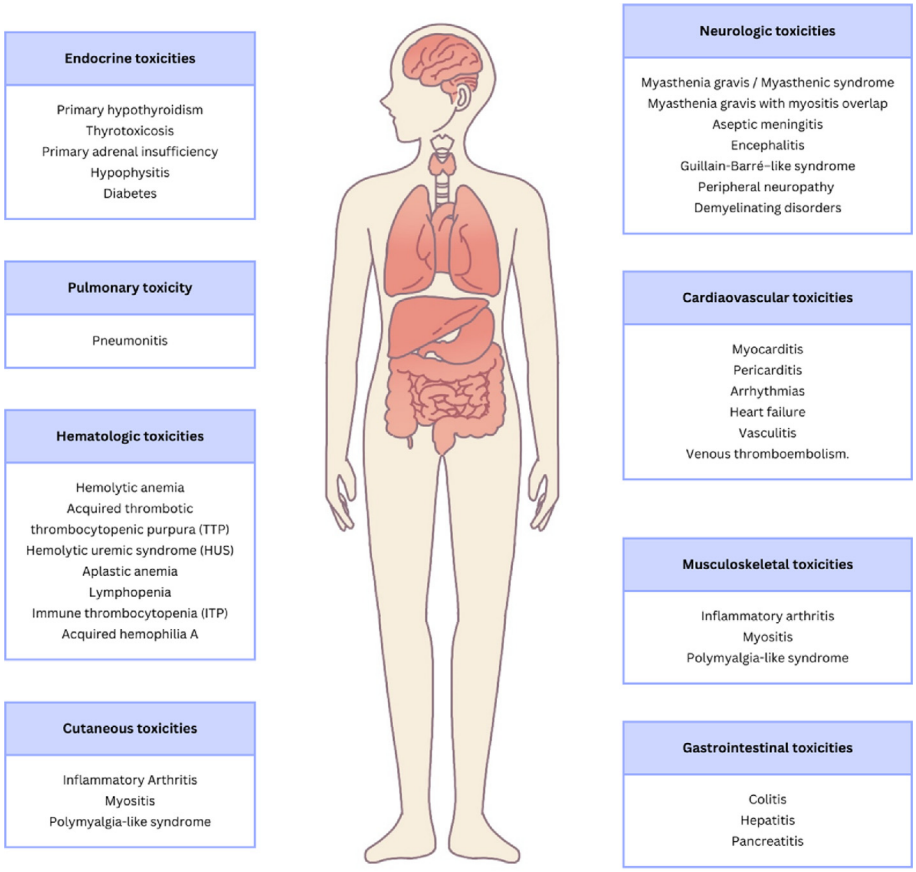

Fig. 1. Organ-specific immune-related adverse events (irAEs) caused by immune checkpoint inhibitors (ICPi).[1]

general, ICPi therapy can be continued for grade 1 toxicities although neurological and cardiac irAE may be exceptions to this rule. In the case of our patient, *de novo* myasthenia gravis (MG) and possible myocarditis were observed 22 days following his pembrolizumab therapy.

3.1. Myasthenia gravis

Neurotoxicity was thought to be uncommon among irAEs but further studies revealed that the incidence rate could be as high as 6.1%.[1] The median time to onset is typically 4 weeks and patients may present with a wide spectrum of disease from benign sensory neuropathies to more serious pathologies such as MG. Neurologic irAEs are more commonly reported among patients receiving PD-1/PD-L1 inhibitors compared to cytotoxic T-lymphocyte–associated antigen 4 inhibitors (CTLA-4), but the incidence rate can further increase among those receiving combination therapy. MG is characterized by disruption of synaptic communication in the neuromuscular junction and patients can present with fluctuating muscle weakness, ptosis, double vision, and dysarthria.[1,3] Workup includes autoantibody testing against AChR, muscle-specific kinase antibody (MuSK), and low-density lipoprotein receptor-related protein 4 (LPR4).[1] If the serologic workup is negative, adjunctive testing such as edrophonium test or neuromuscular junction testing with repetitive stimulation can aid in the diagnosis.[1,4,5]

The severity of the toxicity can be classified from grade 2 to grade 3–4 which correlates to the Myasthenia Gravis Foundation of America (MGFA) severity class I-II and III-V, respectively (see Table 1).[1] MGFA severity class I-II denotes ocular weakness or mild weakness in other muscles. Class III-IV denotes moderate to severe muscle weakness and class V is defined as requiring intubation with or without mechanical ventilation. In the case of our patient who demonstrated grade 3–4 toxicity, the mainstay treatment involves initiating pyridostigmine, corticosteroids, IVIG, and/or plasmapheresis. In refractory cases, rituximab, a monoclonal antibody to CD20, may be used as a third-line agent which can work by depleting B lymphocytes.[1,6,7]

3.2. Myocarditis

Cardiac irAE has also been increasingly recognized although the overall incidence remains low at 0.1%.[1] Cardiac toxicity can manifest as myocarditis, arrhythmias, cardiomyopathy, and pericarditis/pericardial effusion among others.[1,8] When cardiac irAE is suspected, patients must be admitted to the hospital for evaluation and telemetry monitoring.[1] The initial evaluation should include erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), creatine kinase (CK), troponins, NT-proBNP levels as well as chest X-ray, ECG, and echocardiography for assessment of left ventricular function.

Myocarditis is the most prevalent cardiotoxic irAE and can develop after only one or two doses of ICPi.[8,9] Patients may present with wide-ranging symptoms, from asymptomatic cardiac biomarker elevation to life-threatening cardiogenic shock or cardiac arrest.[9] Disease severity can be classified into grade 1 through grade 4 and further ICPi doses should be held even for grade 1 toxicities (see Table 1).[1] Our patient's clinical presentation was consistent with grade 1 myocarditis as he presented with chest pressure and shortness of breath with abnormal cardiac biomarkers but no ECG or echocardiogram abnormalities.

Similar to ICPi-induced MG, treatment strategies involve administration of steroids, IVIG, and plasmapheresis with adjunctive immune modulators in refractory cases.[1,9] However, ICPi-related myocarditis could be fatal despite treatment and the mortality rate can reach up to 50%.[8,9]

Several cases of myocarditis with myositis and/or myasthenia gravis overlap syndrome (IM3OS) have been reported in literature.[10–12] While ICPi-related myocarditis is a rare complication and oftentimes occurs in isolation, IM3OS has been reported in up to 30–40% of cases with a mortality rate as high as 60%.[14] Therefore, it is important for clinicians to have a high index of suspicion for concurrent

Table 1. Grading system of myasthenia gravis and myocarditis caused by immune checkpoint inhibitors (ICPi).[15]

	Myasthenia Gravis	Myocarditis
Grade 1	Not applicable	Abnormal EKG, abnormal cardiac biomarkers
Grade 2	Symptoms that interfere with Activities Daily Living (ADLs) including ocular symptoms and mild generalized weakness	Abnormal screening tests with mild symptoms including chest pain, palpitations, dyspnea, fatigue
Grade 3	Combined with Grade 4, please see below	Moderately abnormal testing or symptoms with mild activity
Grade 4	Weakness that limits walking, any dysphagia even if mild, facial or respiratory muscle weakness, moderate to severe generalized weakness	Moderate to severe decompensation along with use of intravenous medication or intervention required, life threatening conditions

myocarditis in patients presenting with pembrolizumab-induced MG and recognize the potential for fatal outcomes when these conditions co-occur.

4. Conclusions

ICPi has been a breakthrough in the field of oncology and pembrolizumab is one of the most common and effective medications used in this domain. Despite its effective treatment for many cancers, it comes with the risk of irAE. In our case, the patient underwent pembrolizumab treatment for bladder cancer but acquired MG and possible concurrent myocarditis. IM3OS has been recognized in previous case reports and while the pathophysiology remains unclear, it has been shown to be associated with high case fatality rates. As such, patients presenting with one of these irAEs should be screened for concurrent disease so that prompt treatment and supportive management can be initiated.

Conflict of interest

There is no conflict of interest.

References

1. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol*. 2021;39(36):4073−4126. https://doi.org/10.1200/jco.21.01440.
2. Chen L, Han X. Anti−PD-1/PD-L1 therapy of human cancer: past, present, and future. *J Clin Invest*. 2015;125(9):3384−3391. https://doi.org/10.1172/jci80011.
3. Lorenzo CJ, Fitzpatrick H, Campdesuner V, George J, Lattanzio N. Pembrolizumab- induced ocular myasthenic crisis. *Cureus*. 2020. https://doi.org/10.7759/cureus.9192.
4. Takai M, Kato D, Iinuma K, 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. https://doi.org/10.1016/j.eucr.2020.101145.
5. Montes V, Sousa S, Pita F, Guerreiro R, Carmona C. Myasthenia gravis induced by ipilimumab in a patient with metastatic melanoma. *Front Neurol*. 2018;9. https://doi.org/10.3389/fneur.2018.00150.
6. Verma N, Jaffer M, Pina Y, Peguero E, Mokhtari S. Rituximab for immune checkpoint inhibitor myasthenia gravis. *Cureus*. 2021. https://doi.org/10.7759/cureus.16337.
7. Blum S, Gillis D, Brown H, et al. Use and monitoring of low dose rituximab in myasthenia gravis. *J Neurol Neurosurg Psychiatr*. 2010;82(6):659−663. https://doi.org/10.1136/jnnp.2010.220475.
8. Ball S, Ghosh RK, Wongsaengsak S, et al. Cardiovascular toxicities of immune checkpoint inhibitors. *J Am Coll Cardiol*. 2019;74(13):1714−1727. https://doi.org/10.1016/j.jacc.2019.07.079.
9. Palaskas N, Lopez- Mattei J, Durand JB, Iliescu C, Deswal A. Immune checkpoint inhibitor myocarditis: pathophysiological characteristics, diagnosis, and treatment. *J Am Heart Assoc*. 2020;9(2). https://doi.org/10.1161/jaha.119.013757.
10. Pathak R, Katel A, Massarelli E, Villaflor VM, Sun V, Salgia R. Immune checkpoint inhibitor−induced myocarditis with myositis/myasthenia gravis overlap syndrome: a systematic review of cases. *Oncologist*. 2021;26(12):1052−1061. https://doi.org/10.1002/onco.13931.
11. Schwab A, Assaad M, Hamadi R, et al. Pembrolizumab-induced myasthenia gravis and myositis: literature review on neurological toxicities of programmed death protein 1 inhibitors. *J Med Cases*. 2022;13(11):530−535. https://doi.org/10.14740/jmc4008.
12. Ünlütürk Z, Karagülmez AM, Hayti B, Erdoğan Ç. Myocarditis-myositis-myasthenia gravis overlap syndrome depending on immune checkpoint inhibitor. *J Neurosci Rural Pract*. 2023 Jan-Mar;14(1):143−144. https://doi.org/10.25259/JNRP_10_2022.
13. Trinh S, Le A, Gowani S, La-Beck N. Management of immune-related adverse events associated with immune checkpoint inhibitor therapy: a minireview of current clinical guidelines. *Asia-Pacific J Oncol Nurs*. 2019;6(2):154−160. https://doi.org/10.4103/apjon_3_19.
14. Zotova L. Immune checkpoint inhibitors-related myocarditis: a review of reported clinical cases. *Diagnostics*. 2023 Mar 25; 13(7):1243. https://doi.org/10.3390/diagnostics13071243. PMID: 37046461; PMCID: PMC10093455.
15. ASCO Guidelines. *Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy*. American Society of Clinical Oncology Clinical Practice Guideline; 2018.