ABSTRACT

A Re-Challenging Case

Walter Schiffer[1,2], Kathleen Zhang[1,2], Douglas Kyrouac[1,2], Daniel Lenihan[1,2]

[1]Washington University School of Medicine, St. Louis, MO 63110
[2]Barnes-Jewish Hospital, St. Louis, MO 63110

Corresponding author: Walter Schiffer, wschiffe@wustl.edu

Winner at ACP MO Chapter 2019 (not peer-reviewed or edited by this Journal)

Am J Hosp Med 2020 Jan;4(1):2020.006 https://doi.org/10.24150/ajhm/2020.006

INTRODUCTION

Immune Checkpoint Inhibitors (ICI) are associated with multiple cardiotoxic effects. Balancing adverse effects with anti-tumor response poses a challenge to treating advanced cancers. The safety of re-starting ICI therapy after an adverse event is unknown. We present the case of a 58-year-old man with stage IV melanoma ICI-related myocarditis and complete heart block (CHB).

CASE

A 58-year-old man with stage IV melanoma status-post cycle one of ipilimumab/nivolumab was admitted for new-onset shortness of breath. ECG showed new CHB, and his troponin I level was elevated to 2.8. He underwent left heart catheterization (LHC), which did not demonstrate significant coronary artery disease. A cardiac MRI showed no late gadolinium enhancement (LGE). Cardiac biopsy pathology showed myocarditis with positive PD-L1 positive immunostaining. The patient was managed with pulse-dose steroids for ICI-related myocarditis, with resolution of his complete heart block one month later. A permanent pacemaker was placed empirically in anticipation of resuming ICI therapy. Five months later, the patient was re-trialed with pembrolizumab. He received 5 cycles before ICI therapy was discontinued due to tumor progression. He tolerated the therapy well without further serological or clinical evidence of additional cardiovascular adverse effects.

DISCUSSION

ICIs represent a class of chemotherapies that aim to invigorate tumor-infiltrating lymphocytes (TILs) against cancer by targeting PD-1, PDL-1, and CTLA-4, and have demonstrated effectiveness in multiple cancers, including melanoma and non-small cell lung cancer. However, ICIs may have multiple adverse effects on the heart, including myocarditis. Patients who develop myocarditis present with a troponin elevation and abnormal ECG, but may have a normal LVEF. Workup includes cardiac MRI, which may reveal LGE, though it did not in this case. A LHC is performed to rule-out coronary ischemia. Treatment relies on high-dose steroids. What remains unclear, however, is the potential ability to restart ICI therapy after the treatment of ICI-related myocardial toxicity, especially when these therapies represent the last line of treatment. In this case, the patient was successfully treated with steroids leading to a resolution of his arrhythmia and improvement in symptoms. He was able to restart ICI treatment with a second-line PD-1 without

recurrent cardiovascular complications. Interestingly, the patient's lymphocyte count decreased from a normal level of 2K/cumm at the start of ICI use to 0.2 K/cumm after steroid administration, suggesting a possible lack of immunologic reserve, and therefore an inability to mount an auto-immune response.

References

1. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol. 2016; 13: 473–486.
2. Darvin, Pramod, et al. "Immune Checkpoint Inhibitors: Recent Progress and Potential Biomarkers." *Nature News*, Nature Publishing Group, 13 Dec. 2018, www.nature.com/articles/s12276-018-0191-1.
3. Escudier M., Cautela J., Malissen N., et al. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor–Related Cardiotoxicity. Circulation 2017;136(21):2085–7. Doi: 10.1161/CIRCULATIONAHA.117.030571.
4. Johnson DB., Balko JM., Compton ML., et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med 2016;375(18):1749–55. Doi: 10.1056/NEJMoa1609214.
5. Zhang, Lili, et al. "Late Gadolinium Enhancement in Patients with Myocarditis from Immune Checkpoint Inhibitors." *JACC*, Journal of the American College of Cardiology, 19 Mar. 2019, www.onlinejacc.org/content/73/9_Supplement_1/675.
6. Mahmood SS., Fradley MG., Cohen J V., et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol 2018;71(16):1755–64. Doi: 10.1016/j.jacc.2018.02.037.
7. Salem J-E., Manouchehri A., Moey M., et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol 2018;19(December 2018):1579–89. Doi: 10.1016/S1470-2045(18)30608-9.