JACC: CASE REPORTS VOL. 8, 2023

IMAGING VIGNETTE

ADVANCED

CLINICAL VIGNETTE

Case of Myocarditis After Chimeric Antigen Receptor T Cells With Intracardiac Lymphoma

Dae Hyun Lee, MD,[a,b] Michael Jain, MD PhD,[c] Aleksandr Lazaryan, MD, MPH, PhD,[c] Frederick L. Locke, MD,[c] Daniel Jeong, MD,[d] Mohammed Alomar, MD[a,b]

ABSTRACT

Chimeric antigen receptor T cells (CAR-T) therapy is a novel therapeutic approach that modifies T cells to attack cancer cells, including lymphoma. We present a case of large B cell lymphoma with intracardiac involvement treated with CAR-T in a patient who later experienced myocarditis after CAR-T therapy. (**Level of Difficulty: Advanced.**)
(J Am Coll Cardiol Case Rep 2023;8:101634) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Chimeric antigen receptor T cells (CAR-T) therapy is a novel therapeutic approach that modifies T cells to attack cancer cells.[1] Cardiotoxicities such as heart failure, arrhythmias, and cardiovascular death are increasingly recognized complications.[2] Despite this increased recognition, the mechanism of cardiotoxicity remains largely unclear, especially that of heart failure and cardiomyopathy.

A 76-year-old man with a history of relapsed and refractory diffuse large B cell lymphoma, gout, and hyperlipidemia presented for axicabtagene ciloleucel (Yescarta) CAR-T therapy. His F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan, performed a week before CAR-T therapy, showed enhancement of numerous abdominal nodules with skeletal involvement. In addition, there was a strong uptake within the left atrium along the atrioventricular groove (**Figure 1A**), with a maximum standardized uptake value of 9.5 (abnormal ≥2.5). His baseline cardiac workup showed no structural abnormality on echocardiogram, with normal left ventricular ejection fraction and global longitudinal strain −19.1% (normal level ≤−16%) without intracardiac mass (**Figure 1B**). The 12-lead electrocardiogram showed normal sinus rhythm without ST-T changes or Q waves. The baseline troponin-I and B-type natriuretic peptide levels were normal. He experienced grade 2 cytokine release syndrome on day 7 (fever with hypotension), for which he received tocilizumab. He did not have symptoms suggestive of heart failure, acute coronary syndrome, or arrhythmia. His troponin-I level was mildly elevated. A follow-up echocardiogram showed normal left ventricular ejection fraction and abnormal global longitudinal strain (−14.8%). Therefore, cardiac magnetic resonance (CMR) with gadolinium contrast agent was performed on day 15. There was patchy increased T2-weighted signal primarily involving the septum and apex of the left ventricle. The native T1 signal was

From the [a]Division of Cardiovascular Medicine, University of South Florida Morsani College of Medicine, Tampa, Florida, USA; [b]Department of Cardio-Oncology, H. Lee Moffitt Cancer Center, Tampa, Florida, USA; [c]Department of Bone and Marrow Transplant and Cellular Immunotherapy, H. Lee Moffitt Cancer Center, Tampa, Florida; and the [d]Department of Radiology, H. Lee Moffitt Cancer Center, Tampa, Florida, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received September 6, 2022; accepted September 9, 2022.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2022.09.004

ABBREVIATIONS AND ACRONYMS

CAR-T = chimeric antigen receptor T cell

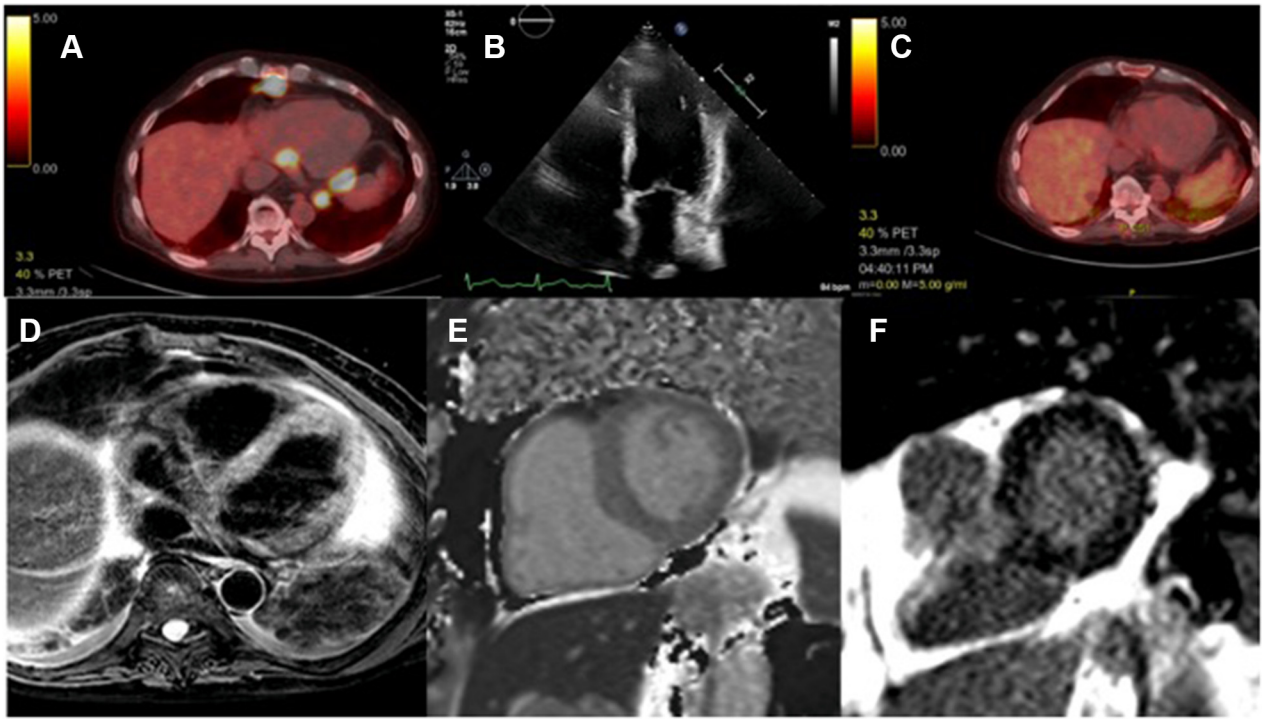
CMR = cardiac magnetic resonance

FDG PET-CT = F-18 fluorodeoxyglucose positron emission tomography/computed tomography

elevated to 1,140 ms. There was patchy midmyocardial and subepicardial late gadolinium enhancement. Collectively, these images were diagnostic of mild acute myocarditis based on the modified Lake Louise criteria (Figures 1D to 1F). A subsequent PET/CT scan for surveillance of cancer at day 30 showed no abnormal uptake within the myocardium (Figure 1C). The patient died 5 months later of progression of his large B cell lymphoma.

To the best of our knowledge, this is the first case of acute myocarditis in the setting of CAR-T evidenced by CMR. We propose intracardiac lymphoma involvement and cytokine release syndrome as potential predisposing factors for CAR-T cell-induced myocarditis. Cardiac lymphoma involvement occurs in approximately 15% to 20% of known lymphoma diagnosis at autopsy. This suggests that intracardiac lymphoma may be a target by the anti-CD19 CAR-T cells. The CAR-T cells target the lymphoma cells and may cause a localized inflammatory cascade involving recruitment of inflammatory cells such as macrophages, neutrophils, lymphocytes, and dendritic cells to the tumor microenvironment.[3] This inflammatory response in the myocardium with localized destruction of lymphoma cells could be detectable by CMR as myocarditis. In conclusion, our case illustrates that CAR-T cell therapy may cause myocarditis, potentially mediated through an on-target effect on the intracardiac lymphoma.

FIGURE 1 Multimodality Cardiac Imaging



(A) Baseline F-18 fluorodeoxyglucose (FDG) positron emission tomography / computed tomography (PET-CT) scan axial fused view of PET-CT scan showing increased FDG uptake in the left atrium posterior/inferior side close to the interatrial septum; maximum standardized uptake value was 9.5. **(B)** Transthoracic echocardiogram apical 4-chamber view before chimeric antigen receptor T cells (CAR-T) therapy showing normal intracardiac chamber size, wall thickness, and not any intracardiac mass or pericardial effusion. **(C)** PET-CT scan 30 days after CAR-T showing resolution of previous focally increased uptake of FDG that was present before CAR-T therapy. **(D)** Cardiac magnetic resonance (CMR) 15 days after CAR-T showing axial T2 SPAIR image with patchy increased T2-weighted signal primarily involving the septum and apex of the left ventricle. **(E)** CMR 15 days after CAR-T showing short axis of native T1 map gray-scale image with increased native T1 signal up to 1,140 ms. **(F)** CMR 15 days after CAR-T showing phase-sensitive inversion recovery delayed gadolinium enhanced image in short axis with patchy midmyocardial and subepicardial late gadolinium enhancement. These images meet all criteria for myocarditis based on the modified Lake Louise criteria.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Jain has been a consulting advisor for Kite/Gilead, Novartis, BMS, and Myeloid Tx; and has received research funding from Incyte and Kite/Gilead. Dr Lazaryan has been a consultant and advisory board member for Kadmon/Sanofi, Humanigen, and Avrobio. Dr Locke has been a scientific advisor role for A2, Allogene, Amgen, Bluebird Bio, BMS/Celgene, Calibr, Caribou, Cellular Biomedicine Group, Daiichi Sankyo, GammaDelta Therapeutics, Iovance, Kite Pharma, Janssen, Legend Biotech, Novartis, Sana, Takeda, Wugen, and Umoja; and has received research funding from Kite Pharma (institutional), Allogene (institutional), CERo Therapeutics (institutional), Novartis (institutional), BlueBird Bio (Institutional), BMS (Institutional), National Cancer Institute, and the Leukemia and Lymphoma Society; and has been a consultant for Cowen, EcoR1, Emerging Therapy Solutions, and Gerson Lehrman Group. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Mohammed Alomar, University of South Florida Morsani College of Medicine, 5 Tampa General Circle, STC 5th floor Cardiology, Tampa, Florida 33602, USA. E-mail: mealomar@usf.edu. Twitter: @mealomar.

REFERENCES

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377:2531-2544.

2. Alvi RM, Frigault MJ, Fradley MG, et al. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *J Am Coll Cardiol*. 2019;74:3099-3108.

3. Giavridis T, van der Stegen SJC, Eyquem J, Hamieh M, Piersigilli A, Sadelain M. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat Med*. 2018;24:731-738.

KEY WORDS chimeric antigen receptor T cell, cytokine release syndrome, intracardiac lymphoma, myocarditis