ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–5
https://doi.org/10.1093/ehjcr/ytad342

CASE REPORT
Coronary intervention

Coronary vasospasm during infusion of CD-19 directed chimeric antigen receptor T-cell therapy: a case report

Jacqueline J. Tao [1]*, Natalia Roszkowska[2], David T. Majure [3], and Syed S. Mahmood [3]

[1]Department of Medicine, NewYork-Presbyterian Hospital/Weill Cornell Medical Center, 525 East 68th St, New York, NY 10021, USA; [2]School of Medicine, Weill Cornell Medicine, New York, NY, USA; and [3]Division of Cardiology, Department of Medicine, Weill Cornell Medicine, New York, NY, USA

Received 7 November 2022; first decision 25 January 2023; accepted 19 July 2023; online publish-ahead-of-print 25 July 2023

Background Cardiovascular events have been reported to occur in one in five patients receiving chimeric antigen receptor T-cell (CAR-T) therapy. Commonly reported effects including cardiomyopathy, heart failure, myocardial infarction (MI), and arrhythmia. Here, we present a novel case of a patient who developed acute ST segment elevations during CAR-T cell infusion.

Case summary A 76-year-old man with diffuse large B cell lymphoma was admitted for an investigational CD-19 directed, autologous CAR-T cell therapy. Less than 5 min into the CAR-T cell infusion, he developed severe chest pain, dyspnea, flushing, hypotension, and tachycardia. Electrocardiogram (EKG) showed inferior ST elevations and reciprocal lateral ST depressions. Emergent coronary angiography revealed mild non-obstructive coronary disease. ST segment changes and patient symptoms resolved after catheterization.

Discussion Given the complete resolution of symptoms and EKG abnormalities in the context of non-obstructive coronary artery disease, this clinical presentation was thought to be most consistent with ST elevation MI due to coronary vasospasm. The mechanism of this vasospasm is as yet not understood and may be related to an anaphylactic reaction or a cardiotoxicity related to the cell therapy agent. As the use of CAR-T therapy continues to expand, there is a need to further characterize the full spectrum of its cardiotoxic effects.

Keywords Acute coronary syndrome • Ischemia • Coronary vasospasm • Cardiooncology • Case report

ESC curriculum 3.2 Acute coronary syndrome • 6.9 Cardiac dysfunction in oncology patients

Learning points

- Chimeric antigen receptor T-cells (CAR-T) are genetically engineered T-cells that express a surface receptor which redirects a T-cell towards a tumor-associated antigen.
- Cardiovascular events are common in patients receiving CAR-T cell therapy and can include cardiomyopathy, heart failure, myocardial infarction (MI), and arrhythmias.
- Ischemia can occur in patients receiving CAR-T and may be attributable to various mechanisms including coronary vasospasm.

* Corresponding author. Tel: +1 212 746 4007, Email: jacqueline.tao26@gmail.com
Handling Editor: Antonios Karanasos
Peer-reviewers: David Blusztein; Marianna Garcia-Saldivia; Doralisa Morrone
Compliance Editor: Megha Agarwal

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy targeting CD-19 is the first Food and Drug Administration approved cell-based gene therapy. CAR-T are genetically engineered autologous or allogeneic T-cells that stably express a surface receptor which redirects a T-cell towards a tumor-associated antigen.[1] The most prevalent toxicities associated with CAR-T therapy include cytokine release syndrome (CRS), a systemic inflammatory reaction due to cytokine release by activated CAR-T cells, and immune effector cell-associated neurotoxicity syndrome. Additionally, cardiovascular events have been reported to occur in one in five patients receiving CAR-T cell therapy, and are associated with high-grade CRS.[2,3] Commonly reported effects include cardiomyopathy, heart failure, myocardial infarction (MI), and arrhythmia.[4] We present a novel case of a patient who developed acute ST segment elevations during CAR-T cell infusion likely secondary to coronary vasospasm.

Summary figure

Time zero	Initiation of CAR-T infusion
4 min after infusion start	Patient develops symptoms concerning for acute coronary syndrome as well as hypotension and tachycardia.
10 min after infusion start	EKG shows inferior ST elevations.
10–50 min after infusion start	Patient receives aspirin 325 mg, intravenous heparin, sublingual nitroglycerin, and morphine. Due to concern for an acute infusion reaction, also receives diphenhydramine, famotidine, Epi-pen, and 1L of normal saline. Started on an epinephrine infusion for hypotension.
2 h after infusion start	Emergent coronary angiography shows nonobstructive coronary artery disease.
1 h post-catheterization	Post-catherization EKG shows resolution of ST changes. Patient symptoms have resolved.
2 days after infusion	Re-evaluated by outside cardiologist. Started on diltiazem 60 mg twice daily and aspirin 81 mg daily.
1.5 weeks after infusion	Decision is made not to re-challenge the patient with CAR-T therapy. Diltiazem is discontinued.
2 weeks after infusion	At oncology follow up, outpatient oncologist confirms the decision not to re-challenge the patient with CAR-T therapy.

Case presentation

A 76-year-old man with stage IV intraorbital diffuse large B cell lymphoma with disease progression despite R-CHOP, RICE, ibrutinib, and radiation, was admitted for an investigational CD-19 directed, autologous CAR-T cell therapy. The patient had no known cardiovascular disease and was not taking any cardiac medications. He had a 50-year smoking history but quit >10 years prior and was otherwise active at baseline with no history of dyslipidemia, diabetes, obesity, or stroke. His baseline ECG and echocardiogram prior to initiation of CAR-T therapy showed sinus bradycardia, normal biventricular ejection fraction, and grade I diastolic dysfunction. He received polatuzumab as a bridging therapy to CAR-T and received standard lymphodepletion with cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2. Less than 5 min into the CAR-T cell infusion, after receiving 0.8 out of 2.2 mL of cell product, he developed severe chest pain, dyspnea, nausea and vomiting, generalized body aches, flushing, and tingling. His blood pressure was 66/47 mmHg, heart rate 130 beats per minute, and temperature 36.4°C. Electrocardiogram (EKG) showed inferior ST elevations with reciprocal lateral depressions (*Figure 1*). He subsequently received aspirin 325 mg, intravenous heparin, sublingual nitroglycerin, and morphine. Due to concern for an acute infusion reaction, he was given diphenhydramine, famotidine, Epi-pen, and 1L of normal saline. Initial fourth-generation troponin I was normal (upper limit of normal is <0.02 ng/mL). Epinephrine infusion was started for hypotension.

Emergent coronary angiography revealed mild non-obstructive coronary disease with ≤30% stenosis in all vessels and TIMI 3 flow (*Figure 2*, Supplementary material online, *Videos A* and *B*). Post-catheterization EKG showed normal sinus rhythm with resolution of ST segment changes. The patient's symptoms completely resolved after catheterization, and he remained hemodynamically stable post-catheterization with no pressor requirement. High sensitivity troponin I trended from 656 to 883 to 425 ng/L (upper limit of normal ≤58 ng/L). One day after the acute reaction, an echocardiogram showed mildly reduced left ventricular ejection fraction of 52%, normal right ventricular function, and no regional wall motion abnormalities. Given the complete resolution of symptoms and EKG abnormalities in the context of non-obstructive coronary artery disease, the patient's clinical presentation was thought to be most consistent with ST elevation MI due to coronary vasospasm. Diltiazem was added to prevent recurrent vasospasm with re-initiation of CAR-T, but was discontinued after the decision was made not to rechallenge the patient with CAR-T given the significant cardiac risks. The patient was subsequently started on metoprolol for cardiomyopathy and was maintained on aspirin 81 mg daily for non-obstructive coronary artery disease.

Discussion

Cardiotoxicity occurs in a significant proportion of patients receiving CAR-T cell therapy. A recent study of 202 CD-19 CAR-T patients found that occurrence of MI, heart failure, or cardiogenic shock was independently associated with an increased risk of mortality.[5] MI occurred in 5% of patients, although none were noted during infusion. Another study of 137 patients receiving CAR-T therapy found that 12% developed a cardiovascular event (cardiovascular death, decompensated heart failure, or arrhythmia), 57% of tested patients had an elevated troponin, and 28% of patients with echocardiograms had newly reduced left ventricular ejection fraction.[4] Notably, all of the above adverse effects occurred in patients with CRS grade 2 or higher. Proposed mechanisms for CAR-T-related cardiotoxicity include acute-phase physiologic changes due to IL-6 mediated inflammation resulting in impaired vascular resistance, systemic fluid retention and myocardial injury. Additional mechanisms may include off-target cross-reactivity of CAR-T cells for striated muscle-specific protein titin (as seen in earlier constructs),[6] or cardiotoxic effects of a lymphodepletion regimen that includes cyclophosphamide. Given the significant risk of cardiovascular events following CAR-T therapy, careful pre-

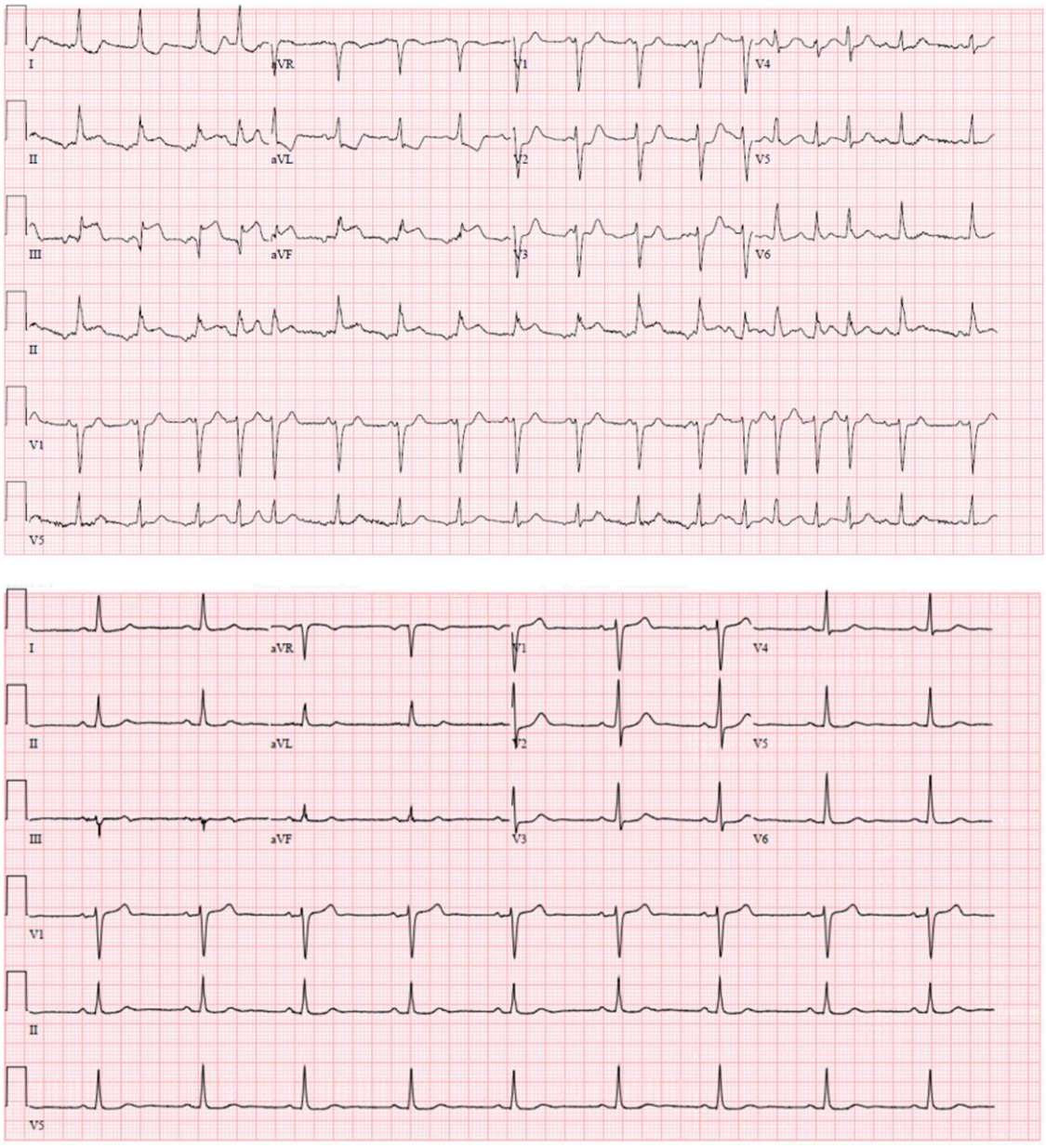

Figure 1 Pre- and post-catheterization EKG. EKG before (top) and after (bottom) catheterization. Pre-catheterization EKG shows inferior ST elevations with reciprocal lateral ST depressions. Post-catheterization EKG shows normal sinus rhythm with resolution of ST changes.

treatment cardiac risk stratification and optimization should be undertaken.[7]

In contrast to prior reports of CAR-T-associated cardiotoxicity, this patient's presentation occurred outside the context of clinical CRS given the immediate onset of symptoms and absence of fever. The timeline of symptom onset within minutes may point away from a direct effect of the CAR-T cell product, which has been found in pharmacokinetic studies to have a maximum expansion time of 10 days.[8] Alternatively, the acute symptoms of flushing accompanied by hypotension, tachycardia, dyspnea, nausea, and vomiting could represent an anaphylactic reaction to the CAR-T infusion. Anaphylaxis has been previously reported in a patient receiving a mesothelin-targeted investigational CAR-T cell therapy, but did not occur until the third infusion.[9] Acute coronary syndromes including coronary vasospasm have been described to occur secondary to anaphylaxis in the phenomenon termed Kounis syndrome, via a mechanism of mast cell activation and cytokine release.[10] Clinical presentations of Kounis syndrome vary widely but can include acute chest pain, ST segment changes, and troponin elevations as seen with this patient. It remains unclear whether the mechanism of coronary vasospasm in this setting was a direct effect of the CAR-T cell product or secondary to an anaphylactic reaction. Finally, another possible etiology includes myopericarditis, though this is less likely given the low elevation in inflammatory markers (CRP 0.74 mg/dL) and symptom resolution without anti-inflammatory agents such as corticosteroids. Though not

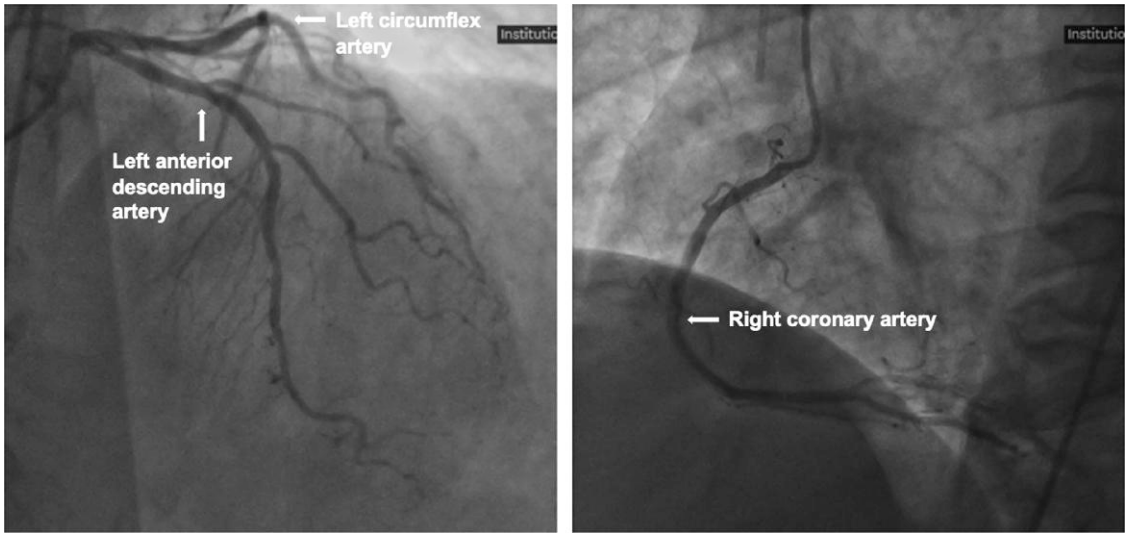

Figure 2 Coronary angiography. Coronary angiography revealed mild non-obstructive coronary disease.

performed in this case, intracoronary imaging techniques may aid diagnostically in cases of acute coronary syndrome by helping to better visualize culprit atherosclerotic lesions or non-atherosclerotic phenomena such as coronary artery dissection.

Other chemotherapies have also been implicated in coronary vasospasm, most commonly 5-fluorouracil. The proposed mechanism involves endothelial damage followed by thrombus formation, ischemia, and direct toxicity to the myocardium. A retrospective study found that patients with fluoropyrimidine-associated vasospasm are generally younger and have lower rates of traditional cardiovascular risk factors.[11] Patients can be successfully rechallenged with the culprit drug to allow for planned chemotherapy completion with pre-treatment with long-acting nitrates and calcium channel blockers. The two lymphodepleting chemotherapies that this patient received, cyclophosphamide and fludarabine, do not have well established associations with coronary vasospasm and are unlikely culprits in this presentation. Cyclophosphamide has historically been associated with left ventricular dysfunction, though a study found the incidence of this was decreased with newer dosing regimens.[12]

Conclusions

We report a case of acute coronary vasospasm in the setting of CAR-T cell infusion with rapid resolution of symptoms following supportive care. The mechanism of this vasospasm is as yet not understood and may be related to a patient-specific anaphylaxis reaction or a cardiotoxicity related to the agent. As the use of CAR-T therapy continues to expand to include new CAR-T formulations, second-line use, and additional cancer indications, there is a need to further characterize the full spectrum of its cardiotoxic effects.

Lead author biography

Dr. Jacqueline Tao is a resident physician in internal medicine at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. She holds an M.D. from Stanford School of Medicine and a B.S. in Bioengineering from Stanford University. She will be pursuing fellowship in hematology–oncology.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Acknowledgements

None.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: S.S.M. has received advisory fees from Nektar Therapeutics, Health & Wellness Partners, Medicure. All other authors have no conflicts of interest to declare.

Funding: S.S.M. is supported by the Glorney-Raisbeck Research Awards in Cardiovascular Diseases from the New York Academy of Medicine.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

References

1. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, *et al.* Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med* 2019;**380**:45–56.
2. Lefebvre B, Kang Y, Smith AM, Frey NV, Carver JR, Scherrer-Crosbie M. Cardiovascular effects of CAR T cell therapy. *JACC CardioOncol* 2020;**2**:193–203.
3. Ganatra S, Redd R, Hayek SS, Parikh R, Azam T, Yanik GA, *et al.* Chimeric antigen receptor T-cell therapy–associated cardiomyopathy in patients with refractory or relapsed non-Hodgkin lymphoma. *Circulation* 2020;**142**:1687–1690.
4. Alvi RM, Frigault MJ, Fradley MG, Jain MD, Mahmood SS, Awadalla M, *et al.* Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *J Am Coll Cardiol* 2019;**74**:3099–3108.
5. Mahmood SS, Riedell PA, Feldman S, George G, Sansoterra SA, Althaus T, *et al.* Biomarkers and cardiovascular outcomes in chimeric antigen receptor T-cell therapy recipients. *Eur Heart J* 2023;**44**:2029–2042.
6. Linette GP, Stadtmauer EA, Maus MV, Rapoport AP, Levine BL, Emery L, *et al.* Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. *Blood* 2013;**122**:863–871.
7. Ganatra S, Carver JR, Hayek SS, Ky B, Leja MJ, Lenihan DJ, *et al.* Chimeric antigen receptor T-cell therapy for cancer and heart. *J Am Coll Cardiol* 2019;**74**:3153–3163.
8. Leahy AB, Elgarten CW, Grupp SA, Maude SL, Teachey DT. Tisagenlecleucel for the treatment of B-cell acute lymphoblastic leukemia. *Expert Rev Anticancer Ther* 2018;**18**:959–971.
9. Maus MV, Haas AR, Beatty GL, Albelda SM, Levine BL, Liu X, *et al.* T cells expressing chimeric antigen receptors can cause anaphylaxis in humans. *Cancer Immunol Res* 2013;**1**:26–31.
10. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med* 2016;**54**:1545–1559.
11. Zafar A, Drobni ZD, Mosarla R, Alvi RM, Lei M, Lou UY, *et al.* The incidence, risk factors, and outcomes with 5-fluorouracil–associated coronary vasospasm. *JACC CardioOncol* 2021;**3**:101–109.
12. Braverman AC, Antin JH, Plappert MT, Cook EF, Lee RT. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. *J Clin Oncol* 1991;**9**:1215–1223.