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CLINICAL CASE CHALLENGES

# Fulminant Cardiotoxicity in a Patient With Cardiac Lymphoma Treated With CAR-T Cells

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Chimeric antigen receptor (CAR) T cells are genetically modified immune cells that target defined tumor surface antigens, hereby enabling T cell-mediated cytotoxicity and, consequently, eradication of cells carrying the respective antigen.[1] The introduction of CD19-directed CAR T cells into clinical practice has revolutionized the therapeutic landscape for B cell malignancies. The armamentarium of currently approved CAR T cell products, and the spectrum of disease indications is rapidly expanding.[2,3] Following antigen recognition, the CAR promotes intracellular signal transduction and amplification, ultimately culminating in T cell proliferation, expansion, cytokine release, and T cell-mediated cytotoxicity.

Yet, the increasing clinical use of CAR T cell products may come in some cases at the cost of potentially life-threatening toxicity. The so far best studied adverse event is cytokine release syndrome (CRS), occurring in more than 90% of cases depending on the product infused.[2-5] While low-grade CRS is regularly reversible and self-limiting, severe CRS occurs in a minority of patients and may ultimately result in severe multiorgan failure. This may be a consequence of cytokine-induced capillary leakage leading to shock with microcirculatory hypoperfusion and end-organ dysfunction.[4,5] Therapeutic options to control CRS include corticosteroids and interleukin-6 receptor antagonists.

Among the complications of CAR T cell therapy, cardiotoxicity secondary to CRS is a complication ranging from arrhythmia, left ventricular (LV) dysfunction, to sudden cardiac death.[6] Although direct "on-target" CAR T cell-mediated cardiotoxicity has been subject of debate, evidence for its existence is lacking.

## CASE DESCRIPTION

A 44-year-old woman presented with a history of recurrent fevers and fatigue. Laboratory evaluation revealed anemia and leukopenia (hemoglobin 9.1 g/dL, leukocyte count 2.4 G/L) and elevated levels of C-reactive protein (153 mg/L), ferritin (30,618 μg/L), and lactate dehydrogenase (4,024 U/L). Following liver and bone marrow biopsy, a diagnosis of diffuse large B cell lymphoma not otherwise specified was made, according to World Health Organization 2016 criteria. After having achieved complete remission to first-line therapy (6 cycles of R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone]), the patient showed early relapse with central nervous system (CNS) involvement, which was treated with salvage chemotherapy (high-dose methotrexate, high-dose cytarabine, rituximab, thiotepa followed by high-dose chemotherapy [carmustine, thiotepa] and autologous stem cell transplantation). Nine months later, the patient presented with extensive

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extranodal disease relapse including CNS and pericardial involvement with alternating supraventricular tachycardia. At this point, lymphocytes were collected for production of CAR T cells. The patient subsequently responded to 2 cycles of R-Hyper-CVAD (1 block A and 1 block B; cyclophosphamide, doxorubicin, vincristine, cytarabine, methotrexate, rituximab) bridging therapy with a morphological response in the CNS (as assessed by magnetic resonance imaging and cerebrospinal fluid analysis); however, positron emission tomography-computed tomography demonstrated progressive disease with signs of tumor infiltration of the pericardium surrounding the right ventricle and the left and right atria. Cardiac magnetic resonance confirmed infiltration of the right atrium and ventricular walls, infiltration of the interatrial septum and atrioventricular (AV) junction, and encasement of the right coronary artery, without evidence of ischemia. Transthoracic echocardiography showed normal LV ejection fraction and a minimal pericardial effusion. Mild concentric remodeling was described in the absence of known arterial hypertension, and echocardiography revealed atrial tachycardia with variable conduction with rates of 100 to 120 beats/min. Due to the patient's frailty and lack of cardiac symptoms, no adenosine test was performed.

**ABBREVIATIONS AND ACRONYMS**

**AV** = atrioventricular

**CAR** = chimeric antigen receptor

**CNS** = central nervous system

**CRS** = cytokine release syndrome

**ICU** = intensive care unit

**LV** = left ventricular

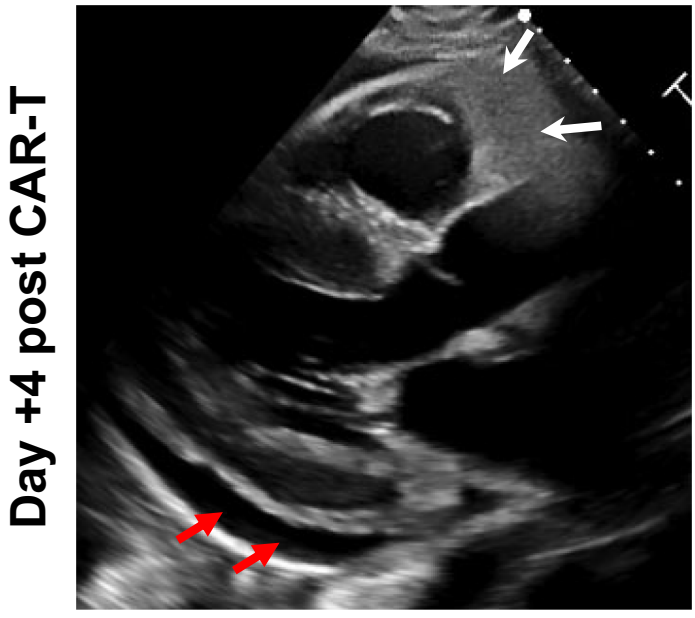
With a CNS response and limited total tumor load in the periphery, we decided to proceed with lymphodepletion with fludarabine (25 mg/m$^2$) and cyclophosphamide (250 mg/m$^2$), followed by infusion of $1.3 \times 10^8$ tisagenlecleucel CAR T cells. Twelve hours after CAR T cell infusion, the patient developed low-grade CRS (fever, tachycardia, and hypotension), which gradually resolved by day +2. On day +4, the patient showed rapid clinical deterioration with fulminant distributive shock and heart failure, prompting admission to the intensive care unit (ICU). Higher-grade CRS was suspected, and the patient received tocilizumab and norepinephrine to maintain her mean arterial blood pressure at 65 mm Hg. Yet, the patient deteriorated and developed hyperlactatemia (12.9 mmol/L) and progressive respiratory failure requiring mechanical ventilation and venovenous hemodialysis, so vasopressin was added to treatment.

Transthoracic echocardiography day +4 post-CAR T cell infusion revealed a rapid and progressive increase in her LV wall thickness (from 10 mm to 15 mm for both the septum and posterior wall), initially with preserved ejection fraction, leading to midventricular cavity obliteration and a restrictive filling pattern (**Figure 1**). Inotropic therapy with dobutamine at 2.5 μg/kg/min was added because of a declining cardiac index to 1.2 L/min/m$^2$ despite aggressive fluid resuscitation. Further expansion of the pericardial effusion seen by echocardiography worsened the filling of both ventricles (**Figure 1**). In addition to tocilizumab, high-dose steroid therapy (500 mg of methylprednisolone daily) was started on day +4.

On ICU admission, the echocardiography showed a regular supraventricular tachycardia (likely atrial tachycardia) and intermittent right bundle branch block at approximately 120 beats/min. The patient then intermittently developed a more rapid, regular supraventricular tachycardia at 150 beats/min, which was felt to be either AV nodal re-entry tachycardia or atrial flutter. On day 3 after ICU admission (day +7 post CAR T), she developed bradycardic atrial flutter with 3:1 conduction at a ventricular rate of 50 beats/min indicative of high-degree AV block, which required placement of a temporary transvenous pacemaker. Within the following days, the patient showed persistent high-degree AV block alternating with atrial tachycardia with intermittent ventricular bigeminy. Concomitantly, an increase in troponin T, which was normal on day -20 prior to administration of CAR T (13 ng/L), was noted on day +4 (143 ng/L) with a peak on day +9 (651 ng/L). As the treatment with steroids and tocilizumab was administered, both perimyocardial lymphoma infiltration with concomitant edema and pericardial effusion decreased. Biventricular function normalized and heart rhythm progressively stabilized, while troponin T levels declined starting from day +10. The transvenous pacemaker was left in place for a total of 12 days and was removed after a 6-day interval free of high-degree AV block or bradycardia. In summary, the patient responded to treatment with steroids and tocilizumab and the treatment for distributive and cardiogenic shock. She was completely off vasopressors after 62 hours and extubated after 10 days. She was then transferred to the hematological step-down unit after 18 days in the ICU, and intermittent hemodialysis was stopped 27 days after admission to the ICU. Unfortunately, 5 weeks after CAR T cell administration, the patient showed CNS relapse on cranial magnetic resonance imaging, while the previously observed cardiac manifestations almost completely resolved on positron emission tomography-computed tomography (**Figure 2**). The patient ultimately succumbed after palliative therapy. The patient provided her written informed consent to publishing her case, and procedures were in line with our local ethics committee's guidelines and the Declaration of Helsinki.

JACC: CARDIOONCOLOGY, VOL. 4, NO. 5, 2022
DECEMBER 2022:708–712

**FIGURE 1 Cardiac Imaging Demonstrating Structural Alterations Day +4 Post-CAR T Cell Infusion**

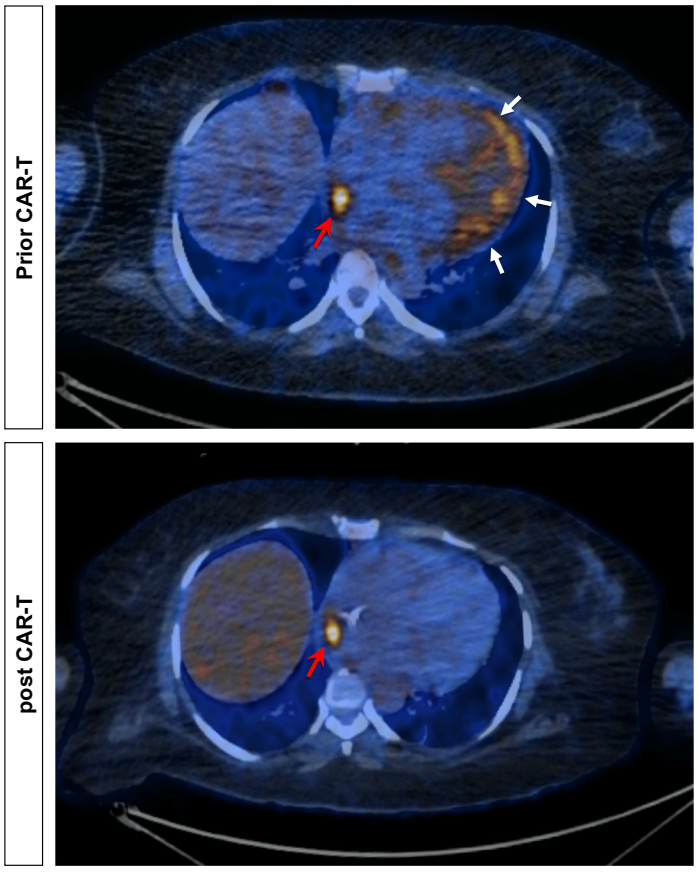



Before chimeric antigen receptor (CAR) T cell therapy, cardiac magnetic resonance revealed lymphoma infiltration along the right ventricle involving the atrioventricular groove. Day +4 after CAR T cell therapy, the parasternal long axis demonstrated severe thickening of the myocardial wall and hypoechogenic edematous myocardium **(white arrows)** as well as a significantly increased pericardial effusion **(red arrows)**. After successful treatment, reduction of the myocardial edema as well as pericardial effusion was seen on transthoracic echocardiography.

Treatment of aggressive lymphoma involving cardiac tissues is a challenge, as both lymphoma and effective treatment with rapid lymphoma cell death may lead to severe and life-threatening myocardial dysfunction and arrhythmias. While cardiac dysfunction associated with severe CRS following CAR T cell infusion has been reported,[6,8] there is only indirect evidence of direct CAR T cell-mediated cardiotoxicity as described in a patient with sudden cardiac death by Kochenderfer et al.[7] To our knowledge, there are no detailed reports of the side effects of CD19-directed CAR T cells in the context of proven myocardial lymphoma infiltration. Here, we present a patient with cardiac lymphoma involving structures of the AV conduction system who was treated with CAR T cells. CAR T cell infusion resulted in a fulminant cardiogenic and distributive shock with rapid thickening of the right ventricular and LV wall with patchy hypo- and hyperechogenic myocardial areas leading to a restrictive cardiac physiology (**Figure 1**). Strikingly, these occurred in close spatial relation to cardiac lymphoma manifestations documented before CAR T cell treatment. At this time point, troponin T levels were highly elevated as a sign of severe cardiac injury. This, together with the development of a pericardial effusion, which likely limited a cardiac compensatory response to the distributive shock due to CRS, resulted in multiorgan failure. Concomitant tachy- and bradyarrhythmia with impaired AV conduction were likely due to edema in the AV conduction system. While the clinical condition of the patient did not allow us to obtain a biopsy to prove CAR T cell infiltration, symptoms correlated with the expansion dynamics of CAR T cells in the blood, suggesting myocardial infiltration with inflammatory cells. As cardiac symptoms resolved thereafter, and a response of the lymphoma was documented without additional lymphoma-directed treatment, it appears less likely that the cardiac manifestations were due to disease progression.

Cancer immunotherapy is associated with a risk of cardiac adverse events (eg, immune checkpoint inhibitor-induced myocarditis).[9] Regarding CAR T cell therapy, a small number of retrospective analyses

**FIGURE 2 Positron Emission Tomography-Computed Tomography Scan Demonstrating Cardiac Lymphoma Manifestation Before and After CAR T Cell Therapy**




Positron emission tomography-computed tomography scan on day -21 before chimeric antigen receptor (CAR) T infusion revealed extensive $^{18}$F-fluorodeoxyglucose uptake as a sign of lymphoma infiltration of the right atrial wall **(red arrow, top)**, the pericardium, and the ventricular wall **(white arrows, upper panel)**, which was also confirmed by cardiac magnetic resonance. On day +35 after CAR T cell therapy, $^{18}$F-fluorodeoxyglucose uptake was markedly decreased, while one previously observed manifestation remained stable **(red arrow, bottom)**.

have reported severe cardiac dysfunction in about 5% to 12% of cases,[6,8] with the majority occurring in patients developing CRS grade ≥3. The underlying pathophysiology remains incompletely understood and has been considered a systemic cytokine-mediated dysfunction of the myocardium and conduction system, as seen in septic conditions.[4] So far, there is no evidence of direct antimyocardial reactivity of CD19-directed CAR T cells. However, the clinical situation may be different in settings in which lymphoma has infiltrated the cardiac tissue. Our case suggests that particularly in patients with cardiac lymphoma infiltration, severe cardiotoxicity can occur, driven by on-target local inflammation by CAR T cells affecting critical cardiac structures such as the conduction system. However, cardiotoxicity may also resolve with treatment of the inflammatory responses. Altogether, we propose that CAR T cell therapy may be indicated in select patients with cardiac lymphoma infiltration. However, these patients may be at particular risk for severe cytokine-associated or cytokine-independent CAR T cell-mediated cardiac adverse events and should therefore be carefully evaluated prior to and closely monitored during treatment. Also, prophylactic or pre-emptive strategies such as interleukin-6 receptor antagonists or early steroids should be considered in such patients at risk. Finally, our case highlights the need for a better mechanistic understanding of CAR T cell therapy's effects—both treatment and toxicity related—on myocardial tissue.

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