



## CASE REPORT

## Severe acute heart failure during or following cytokine release syndrome after CAR T-cell therapy

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## ABSTRACT

Although cardiac dysfunction after chimeric antigen receptor (CAR) T-cell therapy has been increasingly reported, the underlying dynamics and pathogenesis are not well documented. Herein, we describe the clinical presentation and treatment for two patients who developed severe acute heart failure after CAR T-cell therapy. Both cases shared several common characteristics, including the bone marrow involvement at the time of CAR T-cell therapy and early onset of cytokine release syndrome (CRS) with fever developing on the day of CAR T-cell infusion. Patients with early onset and/or severe CRS should be carefully monitored for the possibility of heart failure.

## 1. Introduction

Chimeric antigen receptor (CAR) T-cell therapy targeting CD19 has emerged as a remarkably effective treatment option for relapsed/refractory B-cell acute lymphoblastic lymphoma and diffuse large B-cell lymphoma (DLBCL) [1–3]. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome are the major toxicities of CAR T-cell therapy, with the importance of other toxicities, including cardiovascular toxicities and cytopenia, also increasingly being recognized [4–13]. Among cardiovascular toxicities, tachycardia and hypotension are frequently observed and are probably directly related to CRS. In contrast, cardiac dysfunction, particularly acute heart failure (AHF), is relatively rare. The dynamics of CAR T-cell-associated cardiac dysfunction and its relationship to CRS have not been well documented. Herein, we describe the clinical presentation and treatment for two patients who developed severe AHF after CAR T-cell therapy.

## 2. Case reports

## 2.1. Case 1

A 46-year-old woman was diagnosed with follicular lymphoma, based on the biopsy of an intraperitoneal lymph node. A complete response (CR) was achieved with R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Four years after achieving CR, the patient had a disease relapse, with involvement of multiple systemic lymph nodes. A second CR was achieved after receiving CD20-based radioimmunotherapy, ibritumomab tiuxetan. Three years later, positron emission tomography (PET) and computed tomography (CT) imaging revealed a second relapse of lymphoma with systemic lymph node involvement. She received a combination of obinutuzumab and bendamustine (G-B) as a third line treatment. While lymph node lesions responded to G-B therapy, lactic acid dehydrogenase (LDH) levels increased and bone marrow examination revealed infiltration of large abnormal CD19+ B-cells that lacked CD20 expression. Cytogenetic analysis revealed that lymphoma cells

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harbored the immunoglobulin lambda-MYC translocation, in addition to the IgH-BCL2 translocation. The patient was diagnosed with a large cell transformation of a follicular lymphoma. Although she received hyper-CVAD chemotherapy, in alignment with the aggressive disease features, the response was limited. Finally, she received tisa-cel (tisa-cel) as a fifth line treatment, 11 years after the first diagnosis of lymphoma. At the last assessment prior to tisa-cel infusion (on day -5), lymphoma cells were detected in the peripheral blood (1%) and bone marrow (15%). Prior to tisa-cel treatment, she had received 500 mg/m<sup>2</sup> of doxorubicin cumulatively. An echocardiogram before tisa-cel treatment showed normal cardiac function with a left ventricular ejection fraction (LVEF) of 60%.

The clinical course after tisa-cel infusion is shown in Fig. 1. The patient developed fever on the day of tisa-cel infusion and was diagnosed with CRS grade 1. While she had transient hypotension (systolic blood pressure <90 mmHg), which was compatible with CRS grade 2, tocilizumab was not used at the patient's request. Blood tests on day 9 showed a remarkable elevation in the levels of LDH (9804 U/L) and ferritin (18,842 ng/mL). Although the patient's fever subsided on day 8, she started to complain of dyspnea and required oxygen inhalation due to hypoxia on day 10. Chest radiographs revealed the presence of cardiomegaly and pleural effusion. An echocardiogram, performed on day 15, showed severe global hypokinesis of the left ventricle, with a LVEF of 19%. Typical features of stress cardiomyopathy were not observed. An electrocardiogram showed no apparent findings except for a sinus tachycardia (120 beats/min). The levels of NT-proBNP and troponin were remarkably high; 17,712 pg/mL and 0.054 ng/mL, respectively. Diuretics and low-dose bisoprolol were administered. Echocardiography on day 33 showed an improvement in the LVEF (27%). The patient underwent cardiac catheterization to examine the cause of AHF. Coronary angiography revealed an absence of significant coronary artery disease. Cardiac magnetic resonance imaging showed late gadolinium enhancement, which was compatible with organic damage to the myocardial tissue. Myocardial biopsy revealed non-specific inflammation, with infiltration of T cells and macrophages. She was discharged on day 50 and echocardiogram on day 88 showed further improvement of cardiac function (LVEF 47%).

2.2. Case 2

A 45-year-old man was diagnosed with transformed follicular lymphoma. Although he achieved CR with R-CHOP, the patient relapsed within a year of the last course of chemotherapy. He received R-ACE salvage chemotherapy, consisting of rituximab, cytarabine, carboplatin, etoposide, and methylprednisolone for four courses. After achieving CR, autologous transplantation after high-dose chemotherapy (MEAM, MCNU, etoposide, cytarabine, and melphalan) was performed as a consolidation. Two years later, PET/CT revealed signs of disease relapse and the patient was treated with oral chemotherapy. Five years after the first diagnosis, he received two more lines of salvage chemotherapy (R-ICE and GDP); however, the disease progressed, with 64% of lymphoma cells in the bone marrow. After lymphocyte apheresis for CAR T-cell production, the patient received bendamustine as a bridging therapy. Finally, he received tisa-cel as a seventh line treatment 6 years after the first diagnosis of lymphoma. Prior to tisa-cel infusion (on day -6), lymphoma cells were detected in the peripheral blood (3%) and bone marrow (4.6%). Prior to tisa-cel treatment, he had received 400 mg/m<sup>2</sup> of doxorubicin cumulatively and an echocardiogram showed a LVEF of 54%.

The clinical course after tisa-cel infusion is shown in Fig. 2. He developed a fever 9 h after tisa-cel infusion and was diagnosed with CRS grade 1. On day 2, he developed hypotension and hypoxia; tocilizumab was administered, and dopamine was started to maintain blood pressure. Despite three doses of tocilizumab, the patient additionally required noradrenaline (dopamine 8.0 µg/kg/min and noradrenaline 0.25 µg/kg/min), which was consistent with grade 4 CRS. He received methylprednisolone and was transferred to the intensive care unit.

Echocardiography revealed a rapid decrease in the LVEF—from 54% on day 4 to 19% on day 7. Typical features of stress cardiomyopathy were not observed. An electrocardiogram showed no apparent findings except for a sinus tachycardia (123 beats/min). Moreover, respiratory failure and renal failure had progressed. As a result, mechanical ventilation and continuous hemodiafiltration were initiated on day 6. He also developed a coagulation disorder requiring daily transfusion of fresh frozen plasma to maintain fibrinogen levels >150 mg/dL. With

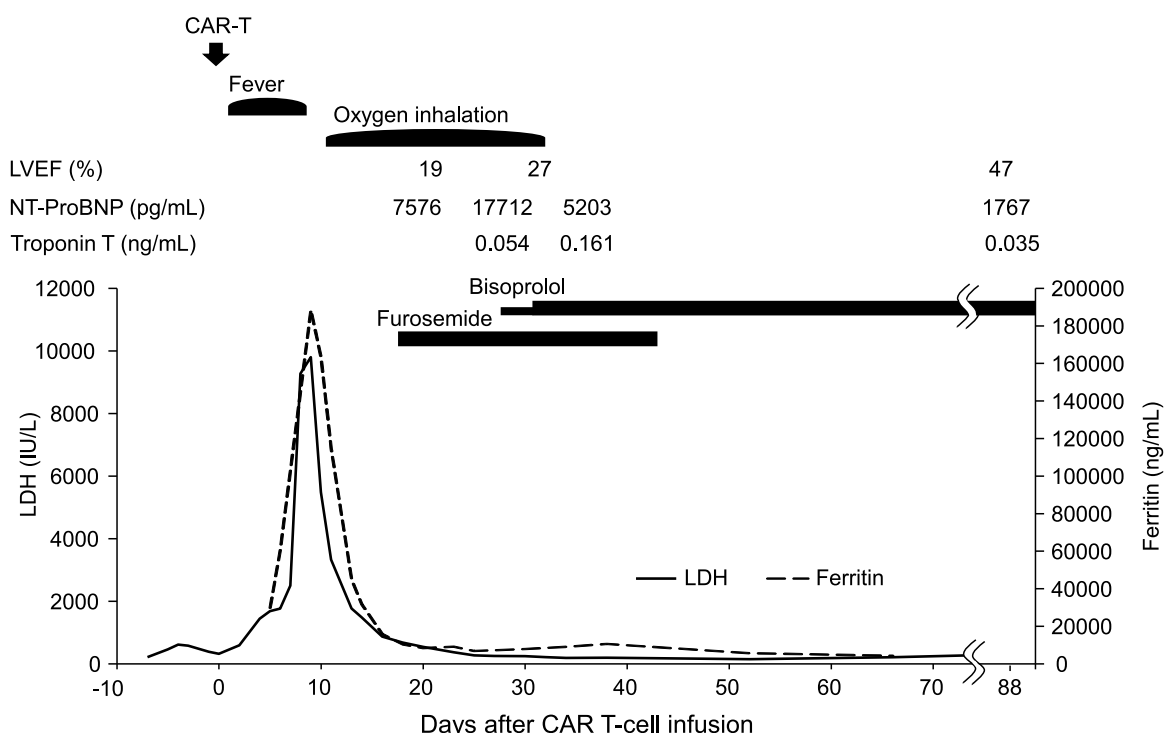


Fig. 1. Clinical course for Case 1.

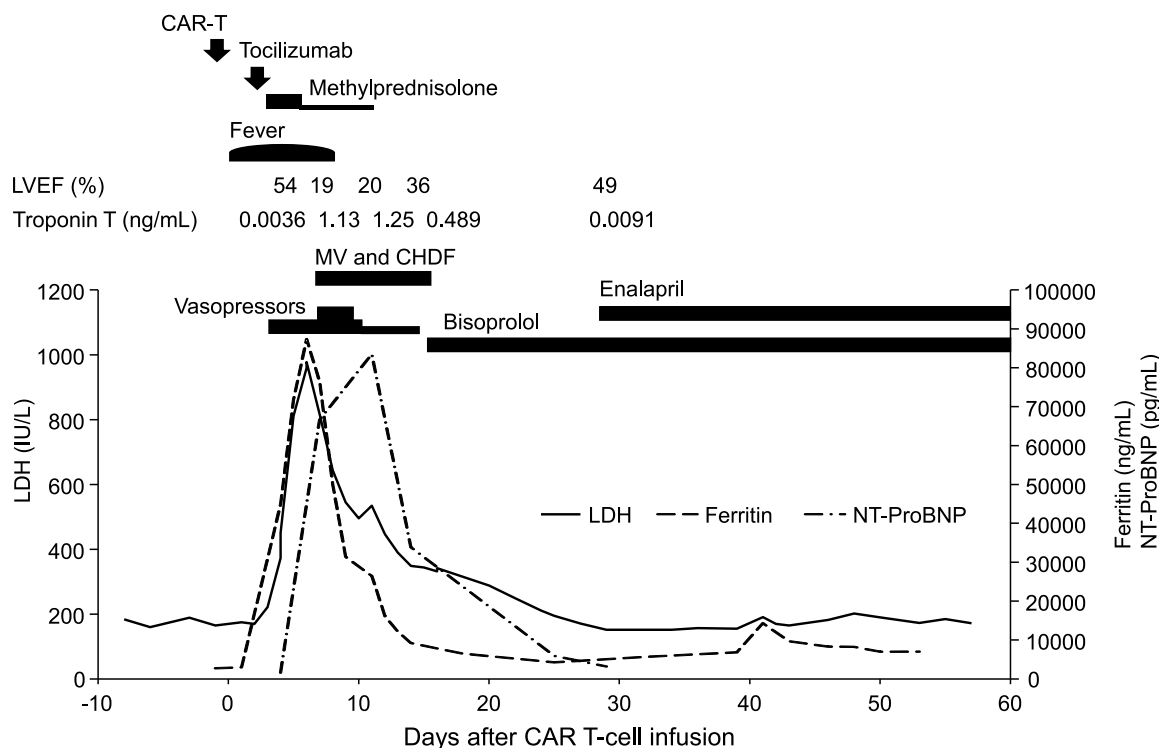


Fig. 2. Clinical course for Case 2. MV; mechanical ventilation, CHDF; continuous hemodiafiltration.

corticosteroid therapy and intensive care, his condition improved. Vasopressor treatment was discontinued on day 13 and mechanical ventilation on day 14. Low-dose bisoprolol and enalapril inhibitors were started subsequently. Echocardiography confirmed a steep recovery of the LVEF—from 36% on day 14 to 49% on day 28.

### 3. Discussion

We report on two patients who developed severe AHF after CAR T-cell therapy. Although tachycardia and hypotension during CRS have been well documented, the risk for AHF is under-recognized. Recently, Shalbi et al. reported that cardiac dysfunction, defined as a > 10% absolute decrease in the LVEF compared to baseline or new-onset of left ventricular systolic dysfunction of grade  $\geq 2$  and a LVEF < 50%, was observed in 6 out of 52 patients [12]. Interestingly, 4 of these 6 patients had grade 3–4 severe CRS. Moreover, Alvi et al. reported an incidence rate of elevated troponin levels and decreased LVEF after CAR T-cell therapy of 54% and 28%, respectively [4].

Interestingly, the two cases of AHF after CAR T-cell therapy that we report on herein shared several common characteristics. Namely, both patients had lymphoma cells in the bone marrow at the time of CAR T-cell therapy and had received several prior lines of treatment before CAR T-cell therapy. Moreover, both patients had early onset CRS with fever on the day of CAR T-cell infusion. Blood tests for both patients showed remarkably high levels of LDH and ferritin after CAR T-cell therapy, which are attributable to tumor lysis syndrome and macrophage activation, respectively. In the clinical course of AHF, hemodynamic decompensation was transient and cardiac function rapidly recovered under standard therapy in both patients. These common characteristics consistently suggest the significant involvement of inflammatory cytokines in the pathogenesis of AHF after CAR T-cell therapy. Indeed, inflammatory cytokines have been shown to play a major role in the pathogenesis of sepsis-induced cardiomyopathy [14, 15]. Moreover, a COVID-19 induced cytokine storm may cause AHF, which can be successfully treated using tocilizumab [16]. Interestingly, the study by Alvi et al. reported that a shorter time from CRS onset to tocilizumab

treatment was associated with a lower rate of cardiovascular events [4]. Alternatively (or in parallel with cytokine-induced toxicity, local endothelial damage and myocardial microangiopathy may play important roles in the pathogenesis. Further studies are warranted to examine the pathological mechanisms of cardiac failure after CAR T-cell therapy.

We note that in addition to the previously mentioned common characteristics, both patients in our case report had received numerous lines of chemotherapy before CAR T-cell therapy, including a cumulative dose of doxorubicin  $\geq 400$  mg/m<sup>2</sup>. Although the echocardiogram before CAR T-cell therapy showed no signs of abnormal cardiac function, it may be possible that the presence of subclinical myocardial injury would increase patients' susceptibility to cytokine-induced AHF.

### 4. Conclusion

In summary, we report on two cases of reversible severe heart failure after CAR T-cell therapy for DLBCL. Patients with early onset and/or severe CRS should be carefully monitored for the possibility of heart failure by biomarkers (troponin and BNP) and echocardiography. Earlier use of tocilizumab may be considered in the patients with the risk of cardiac dysfunction.

### Informed consent

Informed consent was obtained from the patients.

### Declaration of Competing Interest

SY received speaker honoraria from Novartis. Other than this, the authors have no conflicts of interest to disclose.

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