*Open Forum Infectious Diseases*

BRIEF REPORT

# *Trypanosoma cruzi* Reactivation After Chimeric Antigen Receptor T-Cell Therapy

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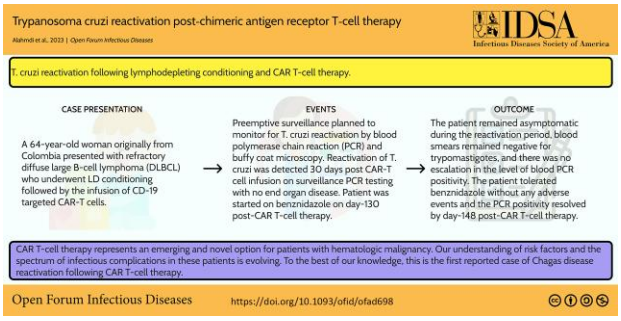
## *Graphical Abstract*




https://tidbitapp.io/tidbits/trypanosoma-cruzi-reactivation-post-chimeric-antigen-receptor-t-cell-therapy/update

**Keywords.** chimeric antigen receptor T-cell therapy; diffuse large B-cell lymphoma; hematopoietic cell transplant; *Trypanosoma cruzi*.

Reactivation of *Trypanosoma cruzi* is well described among solid organ transplant [1] and hematopoietic cell transplant [2, 3] recipients who are chronically infected. Although less commonly reported, reactivation illness can occur in patients who are seropositive, chronically infected, and undergoing chemotherapy for leukemia or lymphoma, as well as those prescribed immunosuppressive therapies for autoimmune conditions [4–6]. Guidelines recommend *T cruzi* serologic screening for donors and recipients of solid organ transplant and hematopoietic cell transplant based on epidemiologic risk, with preemptive monitoring for donor-derived and reactivation illness in the recipients [7–9].

Chimeric antigen receptor (CAR) T-cell therapy has emerged as one of the most promising treatments for B-cell malignancies, including acute lymphocytic leukemia and B-cell lymphoma. These patients are at increased risk of infection due to immunodeficiency related to refractory malignancy, prior cancer therapies, and lymphodepleting conditioning chemotherapy [10]. Furthermore, CAR T cells can induce a range of specific adverse events, such as cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome, and the use of immunosuppressives for the management of these treatment-associated toxicities enhances the global immunodeficiency and associated infection risk observed in CAR T-cell recipients [11, 12]. As the indication for CAR T-cell therapy expands beyond relapsed/refractory B-cell malignancies to include refractory multiple myeloma, the spectrum and risk of infectious complications are expected to evolve [13]. Considering the heterogeneous nature of CAR T-cell recipients, individual patient characteristics become vital in assessing the infectious risk associated with this innovative therapy [12]. Infectious complications following CAR T-cell therapy include predominantly bacterial and respiratory viral infections, but there are increasing reports of *Cytomegalovirus* and fungal infections [10, 12, 14]. Recommendations for infection screening in candidates of CAR T-cell therapy were published in a recent position article, and they include screening for chronic *T cruzi* infection based on the patient's geographic risk [14].

We report the first case of *T cruzi* reactivation in a patient with diffuse large B-cell lymphoma who was seropositive and chronically infected, which occurred following CAR T-cell therapy. This case highlights a global and emerging infectious disease problem due to the increasing use of CAR T-cell therapy in patients with B-cell malignancies and the rising prevalence of Chagas disease in nonendemic areas of the world.

## CASE PRESENTATION

A 64-year-old woman originally from Colombia presented with refractory diffuse large B-cell lymphoma. Her initial treatment for lymphoma included R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) plus intrathecal methotrexate. Subsequently, she received bendamustine plus rituximab and ifosfamide-carboplatin-etoposide plus rituximab for relapsed disease. After 2 years of chemotherapy, her bone marrow biopsy showed residual disease, which led to evaluation for CD-19–targeted CAR T-cell therapy for refractory diffuse

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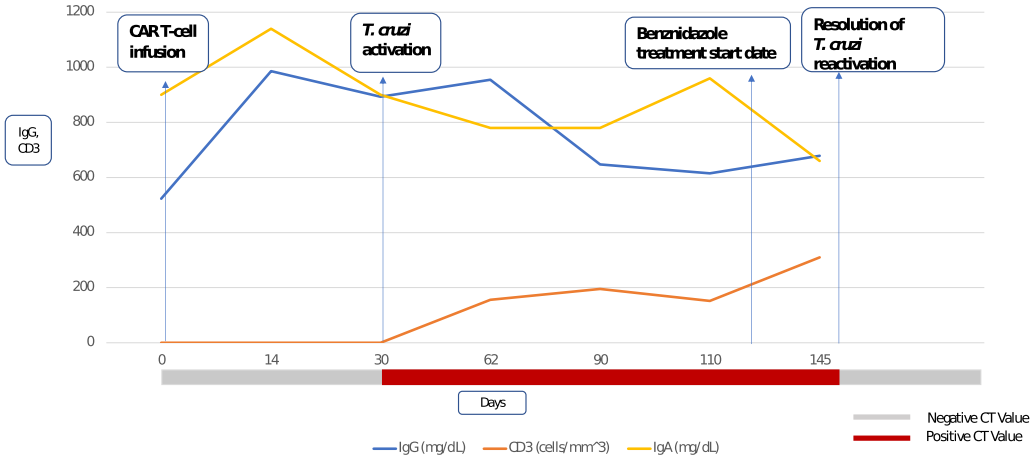


**Figure 1.** Trend of post–CAR T-cell immune markers and *Trypanosoma cruzi* polymerase chain reaction positivity. CAR, chimeric antigen receptor; CT, cycle threshold.

large B-cell lymphoma. The patient underwent lymphodepleting conditioning with lenalidomide, dexamethasone, fludarabine, and cyclophosphamide, followed by the infusion of CD-19–targeted CAR T cells (axicabtagene ciloleucel) [15]. During the treatment, she experienced neutropenia for 9 days, with the lowest absolute neutrophil count of $300 \times 10^3/\mu L$ (range, $300–800 \times 10^3/\mu L$). Before CAR T-cell therapy, 2-step serologic testing for *T cruzi* was performed and resulted positive. Confirmatory *T cruzi* serology was performed at the Centers for Disease Control and Prevention (CDC) Parasitic Diseases Laboratory [15]. To monitor for *T cruzi* reactivation following lymphodepleting conditioning and CAR T-cell infusion, planned preemptive surveillance for reactivation by blood polymerase chain reaction (PCR) and buffy coat microscopy was pursued. Reactivation of *T cruzi* was detected 30 days after CAR T-cell infusion on surveillance PCR testing performed at the CDC Parasitic Diseases Laboratory (see Supplementary Table 1) [15, 16]. Following the detection of reactivation, she was evaluated by cardiology for end-organ disease due to *T cruzi*. The patient was noted to have frequent premature ventricular contractions on her pretreatment electrocardiogram, which persisted without change during the period of reactivation. Transthoracic echocardiography in comparison with pre–CAR T-cell study showed unchanged ejection fraction of 40% and moderate left ventricular dysfunction, with no wall motion abnormalities. Cardiac magnetic resonance imaging showed similar findings and no myocardial scar or fibrosis. These cardiac findings were attributed to toxicity from prior anthracycline-based chemotherapy, and the patient was established in care for long-term management and monitoring of her cardiac function.

The patient's *T cruzi* PCR result remained stable but persistently positive based on CDC laboratory threshold values [15], which led to the initiation of benznidazole dosed at 5 mg/kg/d (300 mg/d divided into 2 daily doses) on day 130 after CAR T-cell therapy. During the course of benznidazole, serial clinical assessment, drug toxicity monitoring (weekly complete blood count and liver enzymes), and blood *T cruzi* PCR plus microscopy were conducted. The patient remained asymptomatic during the reactivation period; blood smears were negative for trypomastigotes; and there was no escalation in the level of blood PCR positivity. The patient tolerated benznidazole without any adverse events, and the PCR positivity resolved by day 148 after CAR T-cell therapy. The trend of parasitologic and immunologic markers in relation to CAR T-cell therapy is illustrated in Figure 1. The patient completed the full 60-day course of benznidazole and, at the last oncology follow-up (722 days after CAR T-cell therapy), was reported feeling well and showed no signs of recurrent malignancy. She remained under cardiology care with no interval issues reported.

## DISCUSSION

*T cruzi* represents a substantial burden among parasitic diseases in the Western hemisphere. In the United States, approximately 300 000 individuals are estimated to be infected with *T cruzi* [17]. While the majority of infections have the indeterminate form of the disease (ie, asymptomatic), around 30% can develop progression over the lifetime to determinate disease forms, most commonly involving the cardiac and/or digestive system [16]. Humoral and cell-mediated immune response to *T cruzi* can be detected in humans who are infected, but the exact mechanism that leads to the transition of an asymptomatic infection to symptomatic Chagas disease is unclear. Experimental data suggest the important function that several cell types and molecules within the innate and adaptive immune response serve to control parasitemia, such as Toll-like receptor signaling pathways, CD4+ and CD8+ T-cell subsets, and interferon γ [18].

*T cruzi* reactivation in our patient was diagnosed on planned preemptive monitoring following CAR T-cell therapy. While CAR T cells themselves can cause profound B-cell immunodeficiency, lymphodepleting conditioning likely played a

significant role, and *T cruzi* reactivation following various types of chemotherapy in patients with hematologic malignancies has been reported [3–5].

Our patient also had low-level stable PCR positivity without the typical manifestations of *T cruzi* reactivation, such as signs of end-organ disease, the presence of *T cruzi* trypomastigotes on peripheral blood smear/buffy coat, or a rising parasite load based on PCR cycle threshold values. Due to the unclear clinical significance of this finding, benznidazole treatment was delayed but ultimately pursued because of the persistent immunosuppressed state after CAR T-cell therapy and the concern for possible progression to symptomatic *T cruzi* infection. While we believe that it was appropriate to treat our patient for *T cruzi* reactivation, we acknowledge that low-level PCR positivity does not necessarily equate to reactivation and that persistent or intermittent low-level PCR positivity has been seen in immunocompetent cases with various stages of chronic *T cruzi* infection [19–22]. As more patients with hematologic malignancy are diagnosed with *T cruzi* infection through targeted pretreatment screening and after CAR T-cell monitoring, we hope that there will be more clarity on the clinical significance of asymptomatic low-level *T cruzi* DNAemia, as seen in our patient, to inform treatment guidance.

In this era of targeted immune-based therapies, CAR T-cell therapy stands as a promising option for hematologic malignancies. Our understanding of the risk factors and microbiologic spectrum of infections in these patients is evolving. As CAR T-cell therapy gains wider adoption, the incidence of infectious complications, including parasitic infections, is expected to rise. Furthermore, due to the increasing geographic diversity in individuals seeking CAR T-cell and other targeted immunotherapies, it is crucial that our clinical management include evaluation for lifetime endemic exposures and the institution of posttreatment preemptive monitoring and/or prophylaxis targeted to endemic pathogens.

To the best of our knowledge, this is the first reported case of *T cruzi* reactivation following lymphodepleting conditioning and CAR T-cell therapy. This case supports the recommendations made by Hill et al [10] of targeted screening based on epidemiologic risk and planned preemptive monitoring following CAR T-cell therapy.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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***Patient consent statement.*** Written informed consent was not obtained from the patient as the study involved presentation of anonymized data that did not reveal the patient's identity. Therefore, the patient's privacy and confidentiality were protected, and no potential harm or risk was posed to the patient.

***Potential conflicts of interest.*** All authors: No reported conflicts.

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