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# Reactivation of Chagas disease in a bone marrow transplant patient: case report and review of screening and management

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## Abstract

We report a patient with an autologous stem cell transplant and history of residence in a Chagas disease (CD) endemic area who developed Chagas reactivation after induction for transplantation. We recommend that patients at risk for CD be screened before transplantation, and patients found to have chronic infection be monitored for reactivation post transplant.

### Keywords

Chagas disease; *Trypanosoma cruzi* ; transplant; parasites; stem cell transplant; reactivation Chagas

We report a patient who underwent autologous stem cell transplantation (ASCT) and had a history of residence in a Chagas disease (CD) endemic area, who developed Chagas reactivation after induction for transplantation.

## Case report

A 54-year-old woman originally from El Salvador, with a history of multiple myeloma diagnosed in 2007, complicated by thoracic and lumbar spine compression fractures, was found to have progression of the myeloma despite chemotherapy and radiation therapy. The patient was scheduled to undergo ASCT as part of her salvage therapy. The patient's medical history and results of her physical examination were unremarkable, without evidence of cardiac, gastrointestinal, or dermatologic disorders.

In October 2010, the patient was admitted for high-dose cyclophosphamide infusion and stem cell harvesting. Following the procedure, the patient recovered without incident

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and was subsequently discharged. Laboratory tests performed as part of her routine pre-transplant evaluation in November 2010 revealed white blood cell count 8.6 cells/$mm^3$, hemoglobin 8.9 g/dL, hematocrit 26.4%, and platelets 35,000 cells/μL. Her metabolic panel, including liver enzymes, was normal.

In addition to the routine laboratory evaluation, the Hematology-Oncology service sent serum samples for CD serologic testing, in accordance with the Foundation for the Accreditation of Cellular Therapy – Joint Accreditation Committee ISCT-EBMT (FACT-JACIE) guidelines (1) that recommend all hematopoietic progenitor cell donors be tested within 30 days before collection for evidence of clinically relevant infection, including *Trypanosoma cruzi*. A serum sample tested at Quest laboratories (Quest Diagnostics, San Juan Capistrano, California, USA) was found to be repeatedly positive for antibody to *T. cruzi* by enzyme-linked immunosorbent assay (ELISA). The Centers for Disease Control and Prevention (CDC) was contacted for guidance on management. CDC recommended confirmation of the diagnosis by additional serologic testing, followed by monitoring for reactivation of chronic infection by performing serial blood smears and polymerase chain reaction (PCR) testing on whole blood samples. A serum sample was tested at the CDC and found to be positive for antibody to *T. cruzi* on both a CD immunofluorescence assay and on the commercial Chagatest ELISA recombinant v.3.0 (Wiener Laboratorios, Rosario, Argentina).

On December 13, the patient received chemotherapy induction with carmustine, etoposide, and melphalan, followed by stem cell reinfusion on December 14, as per the institutional guidelines and protocol for multiple myeloma patients. The patient became neutropenic for 9 days as a result of the chemotherapy conditioning for ASCT. Weekly whole blood samples were sent to the CDC for testing. Samples collected December 14 and December 30, 2010, were positive by real-time PCR, indicating reactivation of *T. cruzi* infection. The PCR detection performed was a combination of 3 real-time PCR assays (2).

The quantitative output of fluorescence thresholds (Ct values) from the real-time PCR assays on subsequent blood samples were compared, and an apparent increase in parasitemia, as indicated by decreasing Ct values in real-time PCRs, was interpreted as evidence of reactivation. Buffy coat exams and hemocultures were performed on all samples that were sent for PCR, but were consistently negative. This finding was expected, as PCR has greater sensitivity and thus becomes positive considerably sooner than microscopy or culture (3).

Advances in PCR techniques have increased the sensitivity of detecting parasitemia in chronically infected individuals. Data from cross-sectional studies (de Freitas et al. [4]) suggest that, in immunosuppressed human immunodeficiency virus-infected individuals, there may be a group of individuals with low-level parasitemia detectable by PCR that does not experience reactivation. However, in the absence of prospective follow-up, it is unclear how many of these patients would have shown increasing parasitemia and how many would have had their parasitemia resolve. The real-time PCR used by the CDC, which is not sensitive for low-level parasitemia, was used in a longitudinal fashion. The decrease in Ct values from December 9 to December 30 represented a 100-fold increase in parasitemia, consistent with reactivation. The real-time PCR became and remained negative

after treatment, further supporting the occurrence of a reactivation event. Testing at multiple timepoints is required to confirm reactivation, although this is preferable to waiting until the much less sensitive parasitelogic techniques can detect reactivation, because permanent tissue damage may already be occurring by the time these tests are able to detect parasitemia (4).

Treatment was initiated with benznidazole at 5 mg/kg/day for 60 days. Samples collected after treatment tested negative by PCR, buffy coat, and culture; subsequent parasitologic testing has remained negative (Table 1), although antibody has persisted for 2 years after transplantation.

## Discussion

To our knowledge, this is the first reported case of reactivation of chronic CD in a bone marrow transplant recipient in the United States. An estimated 300,000 persons living in the United States have chronic *T. cruzi* infection and these numbers are likely to increase with immigration from endemic countries (5).

Some of these chronically infected persons may become solid organ or hematopoietic SCT recipients, either because of progression of cardiac CD or other diseases. When these persons are immunosuppressed to prevent organ or graft rejection, the disruption of the immune systems may result in reactivation of their chronic CD.

Latin American studies report reactivation rates in post-transplant patients by organ type: approximately 9–16% kidney (6), 50–100% heart (3), and 17–40% ASCT and allogeneic hematopoietic SCT patients (7). Reactivation may present as a febrile illness that resembles acute rejection. Untreated, reactivation may result in dermopathy (e.g., panniculitis or nodules), myocarditis (which can result in congestive heart failure or atrioventricular block), or death (7, 8).

Patients with risk factors for CD should be screened for disease before immunosuppression, so that appropriate monitoring for reactivation disease can be implemented. Risk factors for prior infection with *T. cruzi* include birth or long-term residence in an endemic country, or mother's birth or long-term residence in an endemic country, as well as having spent 3 months or more in Mexico or endemic countries of Central or South America (9, 10). Diagnosis of chronic infection relies on positive results on 2 or more different serologic tests.

In 2009, the United States Food and Drug Administration published draft industry guidelines determining donor eligibility of human cells, tissues, and cellular and tissue-based products to reduce transmission of *T. cruzi* infection (11). These recommendations have since been adopted by FACT-JACIE, requiring all hematopoietic progenitor cell donors to be tested 30 days before collection. The Chagas in Transplant Working Group, representing the Disease Transmission Advisory Committee of the United Network for Organ Sharing, recommended targeted *T. cruzi* screening of potential solid organ donors and recipients born in Mexico, Central America, and South America (12). Using these recommendations, some persons who receive transplants might still be at risk for reactivation, such as persons who have

traveled to endemic areas and may have been exposed to *T. cruzi*, persons who have received blood transfusions before the implementation of *T. cruzi* infection blood bank screening in 2007, or persons who have had contact exposure with an infected triatomine bug found in the southern half of the United States, including Texas, California, and Arizona. Infections caused by these exposures are thought to be rare.

Current recommendations for post-transplant monitoring of seropositive patients include routine examination of the transplanted patient for signs or symptoms of reactivation and laboratory testing of weekly whole blood samples by examination of blood smears by microscopy and molecular testing by PCR for the first 2 months, twice monthly for the next month, then monthly up to 6 months; after that, monitoring intervals can be lengthened, and any unexplained illness (e.g., fever of unknown origin) or suspected rejection event would be reason for more frequent monitoring. The recommendations for monitoring for reactivation of CD post transplant are similar to the recently published recommendations by Chin-Hong et al. (12). Close monitoring allows for preemptive therapeutic management, thereby reducing and possibly preventing end-organ damage.

Our case highlights the importance of screening for infection caused by *T. cruzi* in recipients at risk for reactivation of this infection. The PCR testing before SCT was negative, although serologic screening tests were positive. Considering the PCR results that show an increase over time, we thought it was likely reactivation because of immunosuppression, as opposed to intermittent low-level parasitemia of chronic infection. The patient was able to avoid CD and its associated symptoms because of preemptive therapy. This case also illustrates the need to screen potential organ and tissue donors who are at risk for CD, and the need for post-transplant monitoring for this disease.

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**Disclaimer:**

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention.

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**Table 1**

Patient's test results for *Trypanosoma cruzi* infection: pre-transplant through 6 months of post-transplant follow-up

| Date | IFA | ELISA | Culture | Slides | PCR (Ct value) |
|---|---|---|---|---|---|
| 23 November 2010 | Positive (1:512) | Positive (2.422) | NI | NI | NI |
| 2 December 2010 | Positive (1:256) | Positive (2.773) | Negative | Negative | Negative |
| 9 December 2010 | NI | NI | ND | ND | Equivocal (34) |
| 14 December 2010 | NI | NI | Negative | Negative | Positive (32) |
| 30 December 2010 | Positive (1:256) | Positive (2.205) | Negative | Negative | Positive (27) |
| 10 February 2011 | NI | NI | ND | ND | Negative |
| 14 March 2011 | Positive (1:256) | Positive (1.678) | Negative | Negative | Negative |
| 6 June 2011 | Positive (1:256) | Positive (1.12) | Negative | Negative | Negative |

IFA, immunofluorescence assay; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; Ct value, quantitative output of fluorescence threshold; NI, not indicated; ND, not done.