

Case Report

Reactivation of Chagas disease in a heart transplant patient infected by sylvatic *Trypanosoma cruzi* discrete typing unit I

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Abstract

Heart transplantation is an effective treatment for Chagas disease patients with severe cardiomyopathy. However, *Trypanosoma cruzi* reactivation is of great concern. The *T. cruzi* parasite is classified into six discrete typing units (DTUs identified as TcI–TcVI). It is unknown whether there is an association between *T. cruzi* genetic lineages and the different clinical manifestations of the disease. We report the case of a 51-year-old man who received a heart transplantation and presented with a reactivation of the disease. The molecular characterization of the parasite showed that the reactivation was related to specific infection by a DTU I (TcI_{SVL}) parasite.

Keywords: Chagas disease. Organ transplantation. Reactivation.

INTRODUCTION

Chagas disease, an infection caused by the parasite *Trypanosoma cruzi*, has a broad spectrum of clinical manifestations, ranging from asymptomatic infection for several years to symptomatic cardiac disease with potential fatality. Heart transplantation is the last therapeutic option for Chagas disease patients with severe cardiomyopathy. Nevertheless, the immunosuppressive treatment that accompanies transplantation increases the probability of infections, including the reactivation of Chagas disease¹. *T. cruzi* has been divided into six discrete typing units (identified as TcI–TcVI), with a proposed seventh (TcBat) typing unit related to TcI. The role of genetic lineages in the clinical manifestations of the disease is still unknown².

CASE REPORT

A 51-year-old man born in Santander, Colombia was diagnosed with Chagas disease when he was 45 years old. He presented with biventricular dysfunction associated with dilated cardiomyopathy and showed a deterioration of the NYHA

(New York Heart Association) functional class IV, with severe left ventricular systolic dysfunction (ejection fraction=20%), resulting in the decision to perform a cardiac transplantation. The heart was obtained from a 20-year-old man who was brain-dead after an accident. After the postoperation period, he received immunomodulating therapy with prednisone, cyclosporine, and mycophenolatemofetil. During the first three months after surgery, he also received prophylaxis for infections by Cytomegalovirus, *Pneumocystis jirovecii*, and *Aspergillus fumigatus* with valganciclovir, trimethoprim-sulfamethoxazole, and itraconazole.

In asking about his family history, we learned that his mother and two brothers were seropositive for *T. cruzi*. He indicated that he had contact with the vector (known in Colombia as “pito”) in his childhood, and that his childhood home had the physical characteristics associated with the typical habitat of the vectors. He never received etiological treatment for Chagas disease.

Four months after surgery, the patient presented with herpes zoster in the facial region, causing a decrease in visual acuity on the left side associated with chronic pain. Concomitantly, we obtained a positive quantitative polymerase chain reaction (qPCR) result (16 parasites/mL) and started benznidazole. **Table 1** shows the results of the qPCR, enzyme-linked immunosorbent assay (ELISA), and immunofluorescent antibody (IFA) tests performed on the patient in the six years following the heart transplantation.

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Received 14 December 2018

Accepted 15 April 2019

TABLE 1: Results of the serological exams and qPCR test performed on the patient during six years of follow-up after the heart transplant.

Date (d/m/y)	qPCR		ELISA			IFA	
	Result	Parasite load	Result	Absorbance	Index	Result	Titer
09/10/2012	Negative	-	Positive	0.924	3.14	Reactive	1024
16/10/2012	Heart transplantation						
25/02/2013	Positive	16 parasite equivalents/mL	Positive	1.545	5.15	Reactive	1024
25/03/2013	Positive	36.2 parasite equivalents/mL	Positive	2.379	7.93	Reactive	2048
24/04/2013	Negative	-	Positive	2.785	9.28	Reactive	2048
23/05/2013	Negative	-	Positive	2.134	7.11	Reactive	1024
20/05/2014	Negative	-	Positive	2.003	6.68	Reactive	1024
21/06/2015	Negative	-	Positive	1.981	6.6	Reactive	1024
14/06/2016	Negative	-	Positive	1.433	4.78	Reactive	1024
27/04/2017	Negative	-	Positive	1.428	4.76	Reactive	1024
18/06/2018	Negative	-	Positive	1.420	4.70	Reactive	1024

(d/m/y): day/month/year; qPCR: quantitative polymerase chain reaction; ELISA: enzyme-linked immunosorbent assay; IFA: immunofluorescent antibody tests.

DISCUSSION

Cardiac transplantation as an therapy for Chagas cardiomyopathy was initially controversial because the disease has an infectious etiology and systemic involvement. However, it is currently the only therapeutic option for patients in the final stage of cardiac failure¹.

The immunosuppressant protocols to prevent rejection of the transplanted organ have been modified over time. The combination of cyclosporine, azathioprine, and prednisone is one of the most commonly used immunosuppressant therapies in these cases³. Evidently, suppression of the immune response predisposes the reactivation of the acute phase of the disease, which facilitates less-restricted reproduction of intracellular amastigotes. Subsequently, the amastigotes undergo transformation into metacyclic trypomastigote, which invade the circulation and colonize the tissues. This phenomenon has been variably reported, with results from zero to 50% of cases¹.

Reactivation is defined as an increase in parasitemia that can be detected by direct parasitological techniques or PCR even in the absence of clinical symptoms⁴. In other words, reactivation is considered to have occurred in a patient with a positive PCR result if the previous PCR result was negative or showed a lower parasitemia than the current one. This definition is important because the reactivation manifestations are variable, ranging from asymptomatic parasitemia to fever, panniculitis, and less frequently, myocarditis and encephalitis⁴, after which a possible rejection of the transplanted organ has to be as part of the differential diagnosis.

TcI, the *T. cruzi* DTU predominant in Colombia, has two specific genotypes TcI_{DOM} and TcI_{SYL}², which have been found in human infections. Based on information from nuclear microsatellites, the patient was infected with TcI_{SYL}², a genotype associated with outbreak infections. This lineage has not been associated as a risk factor for the reactivation of the disease².

Despite the wide spectrum of manifestations, reactivation rarely causes death and the probability of survival in the short and medium terms are similar among transplanted patients with Chagas cardiomyopathy or idiopathic dilated cardiomyopathy¹. This finding has been attributed to various factors of patients with Chagas disease, including low lung vascular reactivity, low incidence of acute failure of the graft, and sudden death compared with patients with dilated cardiomyopathy due to another etiology⁵. Additionally, the patients also benefit from the fact that benznidazole is acceptably effective in reactivation cases and that surveillance for this special group of patients is stricter¹.

The risk factors associated with reactivation are the use of high and prolonged doses of immunosuppressant agents (such as when transplant acute rejection episodes occur), the development of neoplasias, and the use of mycophenolatemofetil instead of azathioprine as the maintenance immunosuppressive treatment^{1,3}. In addition, it has been shown that premature reduction of immunosuppression, especially with corticoids, improves the survival of these patients because it decreases the incidence of parasite reactivation and the appearance of neoplasias⁵.

It has been established that all Chagas disease patients who undergo transplantation need to be monitored due to the potential risk of disease reactivation, both during the acute and chronic phase of reactivation. This monitoring has to be performed through direct methods such as a thick blood smear, which allows for the observation of the parasite, or PCR^{1,4}.

PCR is the method with the best performance for the detection of *T. cruzi* compared to that of conventional parasitological techniques, and on average, it detects 59 days before observation of clinical signs of reactivation⁶. The versatility of the classical PCR technique has led to a large number of PCR variants; qPCR registers 95.7% sensitivity and 100% specificity during the acute phase of the disease. Pinazo et al. recommend that the reactivation monitoring frequency be established according to the time elapsed since the transplantation⁷, (Table 2); in cases when immunosuppression increases, whether it is due to rejection of the transplant or another cause, the surveillance has to be performed weekly for 60 days, and after that, follow-up reverts to the initial scheme according to the corresponding post-transplantation day.

Benznidazole and nifurtimox are clinically recognized trypanocidal drugs used in the case of reactivation and are active against trypomastigotes and amastigotes. Their efficacy depends on the geographical region where they are applied, probably due to differential susceptibility and geographical distribution of the diverse *T. cruzi* strains⁸. Etiological treatment is indicated for 60 days, but may be extended to 90 days depending on the clinical evolution of the patient^{9,10}. The patients who receive treatment must undergo parasitological exams (PCR) every week for four months after starting trypanocidal therapy to determine its effectiveness. Subsequently, the posttreatment follow-up is restarted. In the case of therapeutic failure or the presence of serious adverse effects that force the interruption of benznidazole or nifurtimox (e.g., leukopenia or neutropenia), Pinazo et al. recommend reintroducing the medication during a second cycle or administering an alternative medication such as posaconazole, whose effectiveness is very low but has a better tolerance⁷.

Although some authors mention that progressive negativization or a decrease in antibody titers are recovery criteria for this infection, this measure is very impractical given the variable timeframe in which these indirect methods test negative is variable for different phases of the disease^{1,4,6,11}.

The clinical case we presented is noteworthy because even five years after the detection of parasitic load by PCR in our patient, the antibody titers remained positive although they tended to decrease progressively. Due to this fact, it has been suggested that the recovery criteria during the chronic phase are not only a steady decrease over time in the antibody titers but also the conversion of the xenodiagnosis from positive to negative or a persistent conversion of *T. cruzi* PCR tests from positive to negative. Our patient complied with this last recovery criterion.

To conclude, it is necessary to highlight that pharmacological prophylaxis treatment during the pre- and postsurgical periods has not been proven to be effective. Nevertheless, it is recommended to administer prophylaxis in cases where *T. cruzi*

TABLE 2: Monitoring frequency for *Trypanosoma cruzi* reactivation according to the time after the transplantation.

Time after transplantation	Frequency
Day 0 - day 60	Once a week
Day 61 - day 180	Every eight weeks
Day 181 and later	Annually

parasitemia is observed prior to transplantation or the patient has an HIV coinfection. Due to the high estimated prevalence of Chagas disease in Colombia¹², it is essential that transplant programs are aware of the risk of *T. cruzi* reactivation and understand the principles of managing this condition to prevent adverse outcomes.

Conflict of Interest

The authors declare that there is no conflict of interest.

Financial Support

This study was funded by Instituto Nacional de Salud de Colombia.

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