



## Acute Chagasic Myocardopathy After Orthotopic Liver Transplantation With Donor and Recipient Serologically Negative for *Trypanosoma cruzi*: A Case Report

F.F. Souza, O. Castro-e-Silva, J.A. Marin Neto, A.K. Sankarankutty, A.C. Teixeira, A.L.C. Martinelli, G.G. Gaspar, L. Melo, J.F.C. Figueiredo, M.M.D. Romano, B.C. Maciel, A.D.C. Passos, and M.A. Rossi

### ABSTRACT

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi*. Chagas disease following solid-organ transplantation has occurred in Latin America. This report presents the occurrence of Chagas disease despite negative serological tests in both the donor and the recipient, as well as the effectiveness of treatment. A 21-year-old woman from the state of Sao Paulo (Brazil) underwent cadaveric donor liver transplantation in November 2005, due to cirrhosis of autoimmune etiology. Ten months after liver transplantation, she developed signs and symptoms of congestive heart failure (New York Heart Association functional class IV). The echocardiogram, which was normal preoperatively, showed dilated cardiac chambers, depressed left ventricular systolic function (ejection fraction = 35%) and moderate pulmonary hypertension. Clinical investigation discarded ischemic heart disease and autoimmune and other causes for heart failure. Immuno fluorescence (immunoglobulin M and immunoglobulin G) and hemagglutination tests for *T. cruzi* were positive, and abundant *T. cruzi* amastigotes were readily identified in myocardial biopsy specimens. Treatment with benznidazole for 2 months yielded an excellent clinical response. At the moment of submission, the patient remains in functional class I. This case highlighted that more appropriate screening for *T. cruzi* infection is mandatory in potential donors and recipients of solid-organ transplants in regions where Chagas disease is prevalent. Moreover, it stressed that this diagnosis should always be considered in recipients who develop cardiac complications, since negative serological tests do not completely discard the possibility of disease transmission and since good results can be achieved with prompt trypanocidal therapy.

CHAGAS DISEASE (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi*, which is transmitted mainly by the insects from the *Triatominae*<sup>1-3</sup> subfamily. Following the so-called “Iniciativa del Cone Sur,” which aimed at Chagas disease control, the vectorial and transfusional transmissions were declared extinct in Uruguay (1997), Chile (1999), and Brazil (2005).<sup>4</sup> However, Chagas disease clearly tends to become ubiquitous due to migrating currents and to the continuous modification of ecosystems. That can be exemplified through the estimate that at least 100,000 carriers of *T. cruzi* infection may reside in the United State,<sup>5</sup> and also through the recent evidence of Chagas disease in the Amazon region.<sup>6</sup>

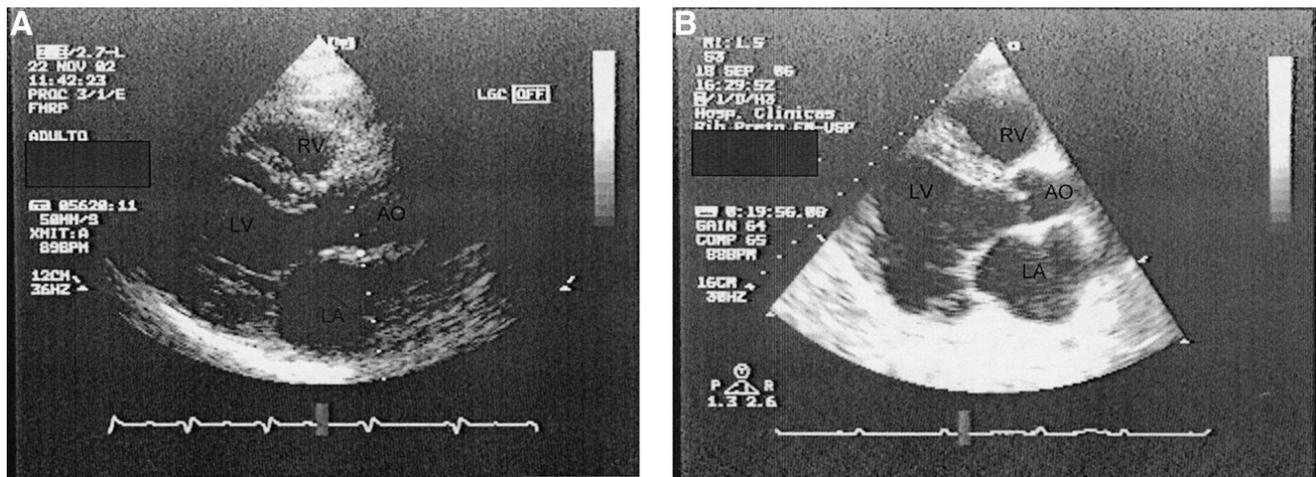
Clinically, the disease includes two phases: acute and chronic. In the acute phase, the manifestations include

characteristic signs in the insect’s sting site and marked symptoms and signs of a systemic infection, such as fever, anorexia, adynamia, malaise, lymph node swelling, hepato-

From the Special Liver Transplantation Unit, Departments of Surgery and Anatomy (F.F.S., O.C.e.-S., A.K.S., A.C.T.), Internal Medicine (J.A.M.N., A.L.C.M., G.G.G., L.M., J.F.C.F., M.M.D.R., B.C.M.), Social Medicine (A.D.C.P.), and Pathology (M.A.R.), Faculty of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil.

Financial support: CNPq, FAPESP, FAEPA, and SUS.

Address reprint requests to Orlando de Castro e Silva, Full Professor, Surgery and Anatomy Department from Ribeirão Preto Medical School, Avenida Bandeirantes, 3.900—CEP 14049-900 Ribeirão Preto—SP—Brasil. E-mail: [orlando@fmrp.usp.br](mailto:orlando@fmrp.usp.br)



**Fig 1.** (A) Pretransplant echocardiographic exam. The parasternal view shows cardiac chambers with normal dimensions, morphology, and function. (B) Echocardiographic examination. In the acute phase of Chagas disease, after liver transplantation, the basal portion of the left ventricular posterior-lateral wall underwent marked thinning, and became akinetic at the motion analysis. RV, right ventricle; LV, left ventricle; AO, aorta; LA, left atrium.

splenomegaly. More severe infection is signaled by cardiac failure due to myocarditis, which is responsible for the rare fatal cases in the acute phase. Such manifestations are accompanied by intense parasitemia and parasite multiplication in the target organs, including the myocardium, the digestive tract, and the nervous system. Nevertheless, the acute phase in most cases is self-limited and may indeed go unnoticed.<sup>1, 7</sup> In the chronic phase, about 60% to 70% of infected individuals remain for life with the latent or undetermined form; they lack clinical or laboratory signs of disease. The other patients characteristically after 10 to 30 years show disease progression, with chronic cardiac and/or digestive manifestations of variable intensity.

In the great majority of patients, the disease is diagnosed in the chronic phase with clinical and pathological manifestations, including striking cardiac arrhythmias and sudden death, heart failure, systemic plus lung thromboembolism,<sup>8</sup> and/or digestive disorders of megaesophagus and megacolon.<sup>7</sup>

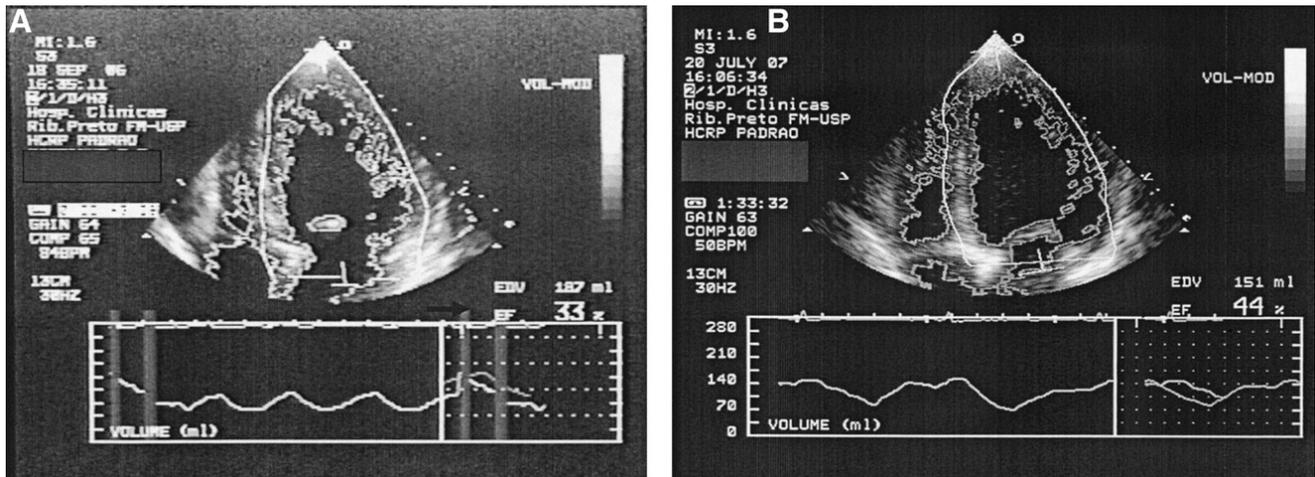
In Brazil, serological tests to scan for *T. cruzi* in blood and organ donors are routinely performed; seropositive donors are discarded for purposes of blood transfusion. However, there are scarce reports on the use of organs (liver) of seropositive donors in seronegative recipients, like "marginal organs."<sup>9,10</sup>

The present article describes a case of acute Chagas disease with severe cardiac involvement after orthotopic liver transplantation from a cadaveric donor. Both donor and recipient were serologically negative for *T. cruzi* prior to the procedure.

#### CASE REPORT

A 22-year-old woman, born in Araraquara, São Paulo State, Brazil, underwent orthotopic liver transplantation. According to standard protocols, both the donor and recipient had undergone serological screening for Chagas disease in the pretransplantation period; both

had been diagnosed as negative through the indirect immunofluorescence reaction method. Ten months after the liver transplantation, which was performed without any complications, the patient was admitted to the hospital because of acute renal failure and atypical precordial pain of >6 hours duration. The electrocardiogram showed sinus tachycardia, diffuse and symmetrical T-wave inversion, sparing only the anterior-septal wall. MB-CK and troponin curves ruled out ischemic heart disease. On the following day, there was striking lung congestion and anasarca leading to the diagnosis of congestive heart failure, functional New York Heart Association class IV. The echocardiogram, which was normal in the period before the transplantation (Figure 1A), showed global depression of left ventricle systolic function with a 35% ejection fraction and marked segmental abnormalities including akinesis of the apex, inferior and posterior-lateral walls, and hypokinesis of the lateral wall. All chambers were dilated, with mitral and tricuspid regurgitation, and there was a mild pericardial effusion (Fig 1B). Immunofluorescence and hemoagglutination (immunoglobulin M [IgM] and immunoglobulin G [IgG]) tests for *T. cruzi* were positive, with titers of 1/512 and 1/156 respectively. Examination of percutaneous myocardial biopsy specimens showed intense myocarditis, with predominant mononuclear infiltrate and presence of *T. cruzi* amastigotes in the myocardial interstitium and in the cytoplasm of mononuclear cells. These findings were confirmed by immunohistochemical methods detecting *T. cruzi* materials in the myocardial interstitium. Standard clinical treatment for heart failure was initiated, and specific trypanocidal therapy with benznidazole (5 mg/kg/d) for 60 days. The patient tolerated the treatment well, showing fast clinical improvement, IgM negativity, and progressive decrease in IgG titers for *T. cruzi*. Currently, the patient has normal liver transplant function and is also asymptomatic from the cardiovascular point of view (functional class 1). The echocardiogram performed 6 months after the specific treatment showed persistence of LV wall motion abnormalities in the posterior-lateral and apical segments. Despite the persistence of these disturbances, with striking thinning and dyskinesia of the posterior-lateral wall, there was some improvement (but not complete recovery) of global systolic function (ejection fraction = 44%), and regression of the pericardial effusion (Fig. 2).



**Fig 2.** Follow-up changes in the echocardiographic examination after specific treatment for Chagas disease. The echocardiographic acoustic quantification technique shows improvement of the left ventricular ejection fraction, but the posterior-lateral wall is dyskinetic and thinned. (P B vs A).

## DISCUSSION

Following strict regulations, potential donors of both solid organs and blood are routinely screened for *T cruzi* infection in Brazil and other countries where Chagas disease is prevalent. When the results of the serological tests are positive these donors are usually discarded for donation purposes, except when there is a written authorization by the recipient. However, over the last years, in Latin America and the United State, one can find diverging results in transplantations of solid organs of seropositive donors in recipients serologically negative for Chagas disease.

In 2002, the United States Centers for Disease Control and Prevention reported the transmission of Chagas disease in three patients who had undergone pancreas-kidney, liver, and kidney transplantations. All were recipients of organs donated by a donor from Central America, who, retrospectively, was supposed to be a carrier of *T cruzi* infection. However, no serological tests had been performed before the donation. The recipient of the liver and pancreas double transplantation died during the treatment for acute Chagasic myocardialopathy. The recipient of the liver died due to sepsis and renal and hepatic failure not related to Chagas disease at 3 months after the transplantation, during the trypanocidal treatment with nifurtimox. The recipient of the kidney underwent treatment with nifurtimox for 4 months, and during the follow-up there was no reactivation of the disease.<sup>11</sup> Barcán et al.<sup>9</sup> reported a case in Argentina, where the liver of a donor who was known to be seropositive for *T cruzi* was transplanted into a seronegative patient displaying fulminant hepatitis. Eighty-four days after the transplantation, acute Chagas disease was diagnosed, and treatment with benznidazole administered for 60 days, but the patient died 18 months after transplantation from infectious complications, which were secondary to the neurological condition. In Brazil, D'Albuquerque et al<sup>10</sup> described six liver transplantations from seropositive donors

into patients with hepatic cirrhosis who were serum negative for Chagas disease. In all these cases, prophylactic treatment with benznidazole was given and in a 42-month average follow-up, the serology was negative in four cases, and two patients died from a cause not related to Chagas disease.

The early diagnosis and timely treatment of both de novo acute disease in previously serum-negative patients and reactivation of Chagas disease in serum-positive immunosuppressed patients are essential for a favorable prognosis in such circumstances. Early diagnosis is based on careful appraisal of the clinical status, parasite isolation, and serological tests based on at least two different methods. The specific treatment with benznidazole or nifurtimox has been shown to be efficient when instituted early in the acute phase or in reactivation of Chagas disease.<sup>3</sup> Untoward effects, such as cutaneous rash, polyneuropathy, myelotoxicity, nausea, vomiting, and, more rarely, hepatotoxicity, have been associated with the use of benznidazole,<sup>8</sup> and can also be, in rare cases, a limiting factor.

The present case shows that infection from *T cruzi* must be investigated in solid organ transplantation when complications of unknown etiology supervene, even when the previous serology tests were negative. Also, it illustrates that the trypanocidal treatment must be instituted as soon as possible to ensure good results in the control of the infection. On the other hand, the use of organs from *T cruzi* positive donors for transplantation into negative recipients should be reserved for situations with no other alternative options, especially in circumstances of organ scarcity and a high prevalence of positive serology for Chagas disease in the general population. However, for this practice to become routine, a larger number of cases ascertaining its safety and efficiency is necessary.

Another noteworthy aspect concerns the possibility of accepting as potential organ donors individuals who have

been screened based only on negative serological examinations. As shown in this report, the possibility of false-negative results points to the necessity of adopting more refined diagnostic criteria, which should comprehend not only serological examinations, but careful consideration of the epidemiological background for Chagas disease and also the active search of the parasite using, for example, polymerase chain reaction methods.<sup>12</sup>

#### REFERENCES

1. Burrattini MN, Turcalo G Jr: Doença de Chagas. In Ramos, OL, Rothschild HÁ, (eds): *Atualização Terapêutica*. 19th ed. São Paulo: Artes Médicas; 1999, p 69
2. Pinto AYN, Valente SAS, Valente VC: Emerging acute Chagas disease in Amazonian Brazil: case report with serious cardiac involvement. *Braz J Infect Dis* 8:454, 2004
3. Santos EO, Canela JR, Monção HCG, et al: Reactivation of Chagas disease leading to the diagnosis of acquired immunodeficiency syndrome. *Braz J Infect Dis* 6:317, 2002
4. Moncayo A, Ortiz Yanine MI: An update on Chagas disease (human American trypanosomiasis). *Ann Trop Med Parasitol* 100:663, 2006
5. Leiby DA, Read EJ, Lenes BA, et al: Seroepidemiology of *Trypanosoma cruzi*, etiologic agent of Chagas' disease, in US blood donors. *J Infect Dis* 176:1047, 1997
6. Coura JR, Junqueira AC, Fernandes O, et al: Emerging Chagas disease in Amazonian Brazil. *Trends Parasitol* 18:171, 2002
7. Meneghelli UG: Chagasic enteropathy. *Rev Soc Bras Med Trop* 37:252, 2004
8. Marin-Neto JA, Simões MV, Maciel BC: Specific diseases: cardiomyopathies and pericardial diseases. Other cardiomyopathies. In Yusuf S, Cairns JA, Camm AJ, et al (eds): *Evidence-Based Cardiology*. 2nd ed. London: BMJ Books, Brit Med Association; 2003, p 718
9. Barcán L, Lunaó C, Clara I, et al: Transmission of *T. Cruzi* infection via liver transplantation to a nonreactive recipient for Chagas disease. *Liver Transpl* 11:1112, 2005
10. D'Albuquerque LA, Gonzalez AM, Filho HL, et al: Liver transplantation from deceased donors serologically positive Chagas disease. *Am J Transplant* 7:680, 2007
11. Chagas disease after organ transplantation—United States, 2001. *MMWR Morb Mortal Wkly Rep* 51:210, 2002
12. Gomes ML, Galvao LM, Macedo AM, et al: Chagas' disease diagnosis: comparative analysis of parasitologic, molecular, and serologic methods. *Am J Trop Med Hyg* 60:205, 1999