Late Chagas’ Disease Reactivation After Heart Transplantation: Where are we standing?

Federico A. Silva, MD, MSc1,*, Adriana M. Serrano-Martínez, MD1, Julio C. Mantilla, MD2, Carlos F. Guerrero, MD3, Luis E. Echeverría, MD3, Mario I Bueno, MD2, Carlos F. Reyes, MD3

Abstract
Chagas disease is endemic in Latin America and has recently spread worldwide. It usually causes an acute heart infection but it may also affect other organs. Some of the cases developing cardiomyopathy go through a chronic phase with severe cardiac failure leading the need for heart transplantation. Those transplanted patients must be immunosuppressed in order to avoid graft rejection, this is a risk factor for the development of early or late chagasic reactivation with central nervous system involvement. We describe the case of a patient with a heart transplant after Chagas chronic cardiomyopathy with CNS compromise by late reactivation of Chagas disease.

Keywords — Chagas disease, chagasic reactivation, encephalitis, heart transplant.

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I. INTRODUCTION
Chagas disease is endemic in Latin America and has spread worldwide. Chagas typically causes acute heart infection, but it may also affect other organs. This disease can become chronic without treatment causing severe cardiac failure leading to severe forms of cardiomyopathy and the need for heart transplantation. *Trypanosoma cruzi* may remain in other tissues after heart transplantation, and immunosuppressant therapy may cause reactivation with either cardiomyopathy or central nervous system (CNS) disease. Therefore, reactivation of the disease should be taken into account in patients with past medical history of cardiac transplantation secondary to chagasic cardiomyopathy and CNS involvement. We describe the case of a patient who underwent heart transplantation secondary to Chagas disease and developed a cerebral mass seven years after his transplant surgery.

II. OUR EXPERIENCE
A 59-year-old male from a rural area of Santander in Colombia presented to the emergency department complaining of asthenia, adynamia, hyporexia and impaired gait within the last week; additionally he referred two episodes of dysarthria lasting one minute each. He had clinical history of hypertension; an ischemic stroke without any sequelae. He received an orthotopic heart transplant seven years earlier secondary to severe cardiac failure (12%). Current treatment included cyclosporine 50 mg twice daily, mycophenolate mofetil (MMF) 500 mg twice daily and prednisolone 5 mg per day, and he had been on peritoneal dialysis within the last year secondary to chronic kidney disease.

His physical examination revealed high blood pressure, dysarthria, diminished muscle strength and hyperreflexia in the lower limbs. A brain magnetic resonance imaging (MRI) performed the second day, showed hyperintense lesions in the splenium of the corpus callosum and periventricular white matter which crossed the midline without border edema in the T2-weighted FLAIR image, suggesting posterior reversible encephalopathy syndrome, hence cyclosporine was suspended (Fig. 1). At day seven, the patient became inattentive and irritable, and the possibility of neuroinfection was considered. Cerebrospinal fluid analysis revealed low glucose level, elevated proteins level and pleocytosis without evidence of microorganisms (Table 1), therapy with acyclovir and amphotericine B were started to cover viral or fungal CNS infections. A brain biopsy was done with an inconclusive result.

At day 12 a transthoracic echocardiogram showed a cardiac output of 50% and left ventricular hypertrophy without any other abnormal findings. At day 15 the patient became stuporous and had acute respiratory failure requiring mechanical ventilation. That same day, fever was observed in the culture of bronchoalveolar lavage material and Piperacillin/tazobactam were started. A follow-up brain MRI performed the same day revealed lesion enlargement. A therapeutic test with...
dexamethasone was given as empiric management for CNS lymphoma (Fig. 1). No improvement was seen with Piperacillin/tazobactam so Meropenem was started two days later. A second lumbar puncture and CSF analysis were performed, with negative results in the culture. At day 25, sedation was withdrawn and the patient remained comatose. Four days later the patient died.

The necropsy revealed a congestive and edematous brain with enlarged, flat gyri, narrow sulci, midline deviation to the left, and a wide necro-hemorragic region in the right occipital lobe. In the microscopic examination the brain had a necrotic area with cysts filled with punctate structures corresponding to amastigotes and the adjacent tissue showed perivascular lymphocytic infiltrate. The heart was enlarged and completely attached to the pericardium which was thickened and whitish in color. The microscopic examination revealed fibrosis and lymphocytic infiltrate, but the valves were histologically normal. Polymerase chain reaction (PCR) in the cardiac and brain tissues identified genetic material of Trypanosoma cruzi 1. Other organs were not involved. As necropsy concluded the patient died of chagasic encephalitis secondary to reactivation of Chagas disease caused by T. cruzi 1 plus a lymphocytic myocarditis and adhesive pericarditis (Fig 2).

The written informed consent to permit the publication of the case, was obtained from the wife of the patient.

### III. DISCUSSION

#### A. Overview of Chagas disease

Chagas’ disease is a trypanosomiasis reported for the first time in a Latin American country by Carlos Chagas in 1909.\(^1\) WHO estimations of Chagas infection cover about seven million to eight million people worldwide.\(^2\)

Chagas’ disease is caused by _Trypanosoma cruzi_, a small flagellated

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Table 1. Biochemical, Hematologic and Cerebrospinal Fluid Laboratory Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Ranges, Adults*</th>
<th>On Admission</th>
<th>4th day</th>
<th>10th day</th>
<th>15th day</th>
<th>25th day</th>
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<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.6 - 1.5</td>
<td>7.64</td>
<td>7.51</td>
<td>8.95</td>
<td>16.36</td>
<td>32.31</td>
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<tr>
<td>Blood urea nitrogen (BUN) (mg/dl)</td>
<td>8 - 25</td>
<td>45.00</td>
<td>40.25</td>
<td>57.61</td>
<td>92.12</td>
<td>76.07</td>
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<tr>
<td>Calcium (mg/dl)</td>
<td>8.5 - 10.5</td>
<td>8.98</td>
<td>9.25</td>
<td>9.08</td>
<td>7.83</td>
<td>7.31</td>
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<tr>
<td>Sodium (mmol/l)</td>
<td>135 - 145</td>
<td>136</td>
<td>141.2</td>
<td>139.9</td>
<td>139.7</td>
<td>142.4</td>
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<tr>
<td>Potassium (mmol/l)</td>
<td>3.6 - 4.8</td>
<td>5.24</td>
<td>4.06</td>
<td>4.69</td>
<td>3.81</td>
<td>4.79</td>
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<tr>
<td>Magnesium (mg/dl)</td>
<td>1.6 - 3</td>
<td>1.88</td>
<td>2.49</td>
<td>2.79</td>
<td>2.74</td>
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<tr>
<td>CRP (mg/l)</td>
<td>0 - 6</td>
<td>23.64</td>
<td>16.7</td>
<td>15.1</td>
<td>62.8</td>
<td>22.2</td>
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<td>TB (mg/dl)</td>
<td>9 - 1</td>
<td>0.4</td>
<td>0.6</td>
<td>0.26</td>
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<tr>
<td>ALT (U/l)</td>
<td>10.45</td>
<td>12.27</td>
<td>41</td>
<td>43.73</td>
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<td></td>
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<tr>
<td>AST (U/l)</td>
<td>10.40</td>
<td>10.8</td>
<td>33.37</td>
<td>39.36</td>
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<td></td>
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<tr>
<td>TSH (mU/l)</td>
<td>0.4 - 4.0</td>
<td>6.05</td>
<td></td>
<td></td>
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<tr>
<td>B12 (mcg/ml)</td>
<td>211 - 246</td>
<td>361.3</td>
<td></td>
<td></td>
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<tr>
<td>Hemoglobin (g/dl)</td>
<td>100 - 400</td>
<td>90</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Hematocrit (%)</td>
<td>41.5 - 15.5</td>
<td>7.4</td>
<td>7.3</td>
<td>8.7</td>
<td>8.8</td>
<td>9.5</td>
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<td>White cells (per mm(^3))</td>
<td>4500 - 15000</td>
<td>4400</td>
<td>3960</td>
<td>4830</td>
<td>15170</td>
<td>14040</td>
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<tr>
<td>Neutrophils (%)</td>
<td>40 - 42</td>
<td>65.5</td>
<td>78.6</td>
<td>70.9</td>
<td>96.5</td>
<td>89.6</td>
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<td>Lymphocytes (%)</td>
<td>22 - 44</td>
<td>7.9</td>
<td>10</td>
<td>14.3</td>
<td>21.4</td>
<td>5.7</td>
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<tr>
<td>Platelets (per mm(^3))</td>
<td>150000 - 450000</td>
<td>229000</td>
<td>155000</td>
<td>229000</td>
<td>155000</td>
<td>235000</td>
</tr>
<tr>
<td>Cerebrospinal Fluid</td>
<td>39</td>
<td>91.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose level (mg/dl)</td>
<td>155.41</td>
<td>146.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein level (mg/dl)</td>
<td>155.41</td>
<td>146.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White-cell count (per mm(^3))</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Reference values are affected by many variables, including the patient population and the laboratory methods used. BUN: Blood Urea Nitrogen, CRP: C-Reactive Protein, TB: Total Bilirubin, ALT: Alanine Amino-Transferase, AST: Aspartate Amino-Transferase, TSH: Thyroid Stimulating Hormone.

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Figure 1. Magnetic resonance imaging studies performed during hospitalization.

At day 2 of hospitalization the axial T2-weighted FLAIR imaging [panel (a)] shows hyperintensity in the periventricular white matter, surviving and compromising corpus callosum. Coronal T2-weighted FLAIR imaging [panel (b)] confirms the involvement of the splenium of the corpus callosum. Sagittal T2-weighted image [panel (c)] shows the impairment of the midline at the splenium. At day 12 of hospitalization the axial T2-weighted FLAIR image [panel (d)] revealed a hyperintense lesion involving both lateral ventricles and the corpus callosum. Coronal T2-weighted FLAIR image [panel (e)] shows extension of the hyperintense lesion over the lateral ventricles’ floor and corpus callosum splenium. Sagittal T2-weighted image [panel (f)] confirms enlargement of the lesion.
protozoan from the family Trypanosomatidae and the genus Trypanosoma from the American continent, which began as an enzootic infection many million years ago and then adapted to humans. The intermediate vectors are insects from the family Reduviidae and the subfamily Triatominae; among them the species of main importance for T. cruzi transmission in humans are the hematophagous insects Triatoma infestans and Rhodnius prolixus since their niche is close to human dwellings. In its vital cycle, the parasite enters the guts of the insect and transforms into epimastigote, a transition form, to divide itself and produce more parasites. Then it becomes trypomastigote, a flagellated form, to be transmitted to humans through the feces of the vector. When the vector gets in contact with a human, it deposits its parasite-carrying feces over the human skin. Already inside the human’s body, the parasite transforms once more, into an amastigote, the intracellular form and before exiting the cell, if uncontrolled by the host’s immune system, it becomes a trypomastigote to circulate through the blood stream and infect other organs. The parasite is also transmitted from mother to child, by blood transfusion, intravenous drugs usage, ingestion of contaminated foods or drink, and organ transplantation.

B. Chagas and heart transplantation

Chagas’ disease in general terms produces an acute cardiomyopathy, which progresses to heart failure with high mortality rate. Refractory long term management of heart failure is the third indication worldwide for transplantation. Despite the fact that an active infection is contraindication for transplantation, a better outcome in patients with chagasic cardiomyopathy has been demonstrated, proved by a better survival rate at eight years of >50%.

Indications for heart transplantation in chagasic patients were proposed in 2008 by Bestetti et al. They described certain conditions due to cardiac dysfunction in patients with Chagas disease as potential indications for heart transplantation, because they are the principal predictors of mortality in these patients. They are the lack of beta-blocker use, hyponatremia, left ventricular ejection fraction under 31%, New York Heart Association Class IV, digoxin use, maximal oxygen consumption rate <10 mL/kg/min at cardiospirometry and patients receiving implantable cardioverter-defibrillator therapy with a clustering of four or more shocks a day.

Immunosuppression protocols in patients with heart transplant used to prevent allograft rejection in transplanted patients have changed through time. The most effective and less harmful protocol was triple therapy with cyclosporine, azathioprine and prednisone. In the last decade MMF has been added to the protocol replacing azathioprine, due to its lower rejection and mortality rates, but some studies have demonstrated higher incidence of side effects.

C. Complications after heart transplantation

Complications either derived from surgery, the transplant itself, or immunosuppression, are to be expected both in the short and long term. Among general complications graft rejections are the most catastrophic with 70% of patients having at least one moderate to severe rejection episode. Other complications include infection 70% of patients; neoplasia may present; and finally reactivation of Chagas’ disease (27% to 90% of patients). Studies done to determine risk factors for Chagas’ disease reactivation, and the number of graft rejection episodes (HR 1.31; CI 95% 1.06-1.62), the development of neoplasms (HR 5.07; CI 95% 1.49-17.20), and the use of MMF as immunosuppressant agent (HR 3.14; CI 95% 1.00-9.84) have proved to be the most important. Another study comparing two immunosuppression protocols, azathioprine against MMF, showed that patients treated with MMF had a higher frequency of chagasic reactivation (HR 6.06; p < 0.0001) and had an earlier episode occurrence compare to the other group.

Figure 2. Pathological studies and polymerase chain reaction

Panels (a) and (b) show an intraparenchymatous hemorrhagic lesion of the white matter at the right hemisphere. Also an ipsilateral left deviation of the middle line and total ventricular collapse are observed. In panel (c) (hematoxylin-eosin; 100x), lymphocyte infiltrate can be seen within the wall of the vessel. Panel (d) (100xC) shows intracytoplasmic amastigotes (approximately 3 mm in diameter) in the brain tissue (arrow). Panel (e) corresponds to lineage typing through agarose gel electrophoresis of PCR products generated by amplification of gene sequences of DNA from the patient. DNA from the reference strain for T. cruzi 1 was used as the positive control in line 4. Line 1 corresponds to water, line 2 is a weight marker. Lines 5 to 10 show cardiac tissue, and lines 11 to 12 brain tissue, which are positive for T. cruzi 1.
D. Pathophysiology of chagasic reactivation

While it is still uncertain, there are some theories about the pathophysiology of chagasic reactivation. The most important relating to parasite persistence refers to the parasite remaining in a quiescent form inside some cells, to emerge later and cause a reactivation of the disease. A second theory, the unified neurogenic theory, explains why there is a loss of neuronal cells in the autonomous nervous system leading to impairment of neurohormonal circuits which conduces to catecholamine toxicity, hence heart failure and also megaesophagus and megacolon. A third theory about autoimmunity, suggests that lymphocytes immunized by T. cruzi produce a crossed cytotoxic reaction against myofibers and neuronal cells of the autonomous nervous system. This might happen despite antiparasitic treatment.\textsuperscript{3,9}

E. Neurological features

Chagas’ reactivation might present in many organs such as heart, liver, skin, and the CNS.\textsuperscript{8,9} Cerebral Chagas may present in different forms, the acute one characterized by encephalitis causing alteration of consciousness state, focalization or seizures, usually associated with myocarditis. The chronic nervous form presents with minor neurological deficits and its histopathology shows inflammatory brain nodules without parasites, which may also occur as ischemic changes due to cardiomyopathy. Finally, reactivation presenting as encephalitis, or a tumor-like form called brain ‘chagoma’. The first one is characterized by nodules with a necrotizing center causing cephalalgia, vomiting, seizures, neurological focalization or even fever. The “chagoma” is a sole lesion usually localized in the frontal lobes debuting more often with focalization.\textsuperscript{12-15} To our knowledge few cases of CNS reactivation of Chagas’ disease after heart transplantation have been reported and they were seen within the first two years after surgery.\textsuperscript{7,11,16}

F. Diagnosis

Diagnosis of Chagas’ disease in its acute phase is made by simple methods such as direct examination of peripheral blood, blood concentration techniques or haemoculture, and more recently using polymerase-chain reaction (PCR). Techniques like complement fixation, indirect hemaglutination assay, indirect immunofluorescence assay, immunoenzymatic assay, radio-immuno-precipitation assay depend on the presence of IgG antibodies, reflecting chronic infection. These serology techniques, as well as PCR are used when a clinical suspicion of Chagas’ disease re-activation cannot be proved by direct methods.\textsuperscript{8,15,17,18} In the CNS, chagasic involvement can be detected through lumbar puncture demonstrating trypomastigotes in the cerebrospinal fluid or amastigotes in a brain biopsy specimen.\textsuperscript{13-15} In some cases, monitoring for chagasic reactivation after cardiac transplantation is a routine; it is usually done by direct observation through hemocultures, xenodiagnosis and Buffy-Coat every four months.\textsuperscript{8} In CNS compromise the brain MRI shows single or multiple contrast enhancing nodular lesions, measuring several centimeters, often affecting the white matter of the brain hemispheres and sometimes cerebellum, brain stem and spinal cord.\textsuperscript{4}

Differential diagnosis should be made including infectious diseases, brain tumors and other pathologies affecting the CNS in the context of immunosuppression, which includes toxoplasmosis, mycobacteria, fungi, progressive multifocal leukoencephalopathy, CNS primary lymphoma, high grade gliomas, and metastases whose radiologic findings are similar to those of cerebral Chagas.\textsuperscript{3,14}

G. Treatment

Nifurtimox and benznidazole have been used in the acute phase of Chagas’ disease treatment. Benznidazole has shown more efficiency compared to nifurtimox and has less adverse events.\textsuperscript{19} In a non-randomized open label long term study reported in 2006, a group of patients was assigned to either treatment with benznidazole or no treatment at all. Negative seroconversion and a minor frequency of disease progression were more frequently seen in treated patients.\textsuperscript{20} These results indicate that such treatments do not eradicate the parasite.\textsuperscript{3} Other medications such as allopurinol have been used, but they have not shown any additional benefits.\textsuperscript{18} Prophylaxis use in transplant recipients is debatable; some authors consider it when the organ comes from a healthy donor.\textsuperscript{5} There is a single case report of a heart transplant recipient patient with Chagas’ encephalitis reactivation, who was treated with benznidazole and had improvement of symptoms; the repeated MRI in this patient showed resolution of the lesion. This finding makes important early identification of this rare complication given the possibility of a good outcome with therapy.\textsuperscript{16}

H. Prognosis

Prognosis of patients with chronic Chagas’ disease is not good. Viotti et al performed a study to establish indicators of progression of chagasic cardiomyopathy. They found that variables such as age at admission >50 years-old, systolic diameter of the left ventricle >40mm, intraventricular conduction abnormalities, sustained ventricular tachycardia and treatment with benznidazole are prognostic variables for chronic chagasic myocarditis progression.\textsuperscript{21} Patients without heart transplant have a low survival rate of 50%, 25%, and 0% at two, four, and eight months respectively; whereas patients undergoing heart transplantation have a better survival rate (83%, 71%, and 57% at one, four, and eight years respectively).\textsuperscript{8,9}
IV. CONCLUSION

The number of heart transplants is rising and Chagas’ disease has become the third most frequent indication for heart transplantation in the world and the first in some hospitals. There are few cases of chagasic reactivation with CNS involvement reported worldwide and they have appeared in patients within the following two years after transplantation. Chagas reactivation may occur even several years after heart transplant surgery as described in the case reported. This case highlights the importance of awareness of Chagas’ reactivation after heart transplantation.

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REFERENCES


