Comparative Histopathology of Endomyocardial Biopsies in Chagasic and Non-Chagasic Heart Transplant Recipients

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Background: Heart transplantation has been an option for the treatment of chagasic (C) cardiomyopathy despite difficulties concerning the control of rejection and reactivation. The parasite-host interaction under the influence of immunosuppressive therapy may affect the immunological response to the graft in a pattern different from that in non-chagasic (NC) patients. The aim of this study was to compare the major histopathological features in heart transplantation in C and NC patients.

Methods: We studied 293 endomyocardial biopsies from two groups of heart transplanted patients, including 18 C and 15 NC. Both groups had identical surgical and clinical procedure except immunosuppressive therapy was lower in C patients. The histopathological parameters evaluated were the Quilty effect, rejection, C myocarditis reactivation, fibrosis, hypertrophy, and ischemia. In addition, lymphocytic cellular infiltration of myocarditis due to rejection or reactivation was immunophenotyped in the biopsies of both groups with rejection grades 3 to 4, in biopsies with signs of reactivation, and in fragments of the receptor heart with chronic C myocarditis. A search for Trypanosoma cruzi was performed in all biopsies in the C group in which lymphocyte immunophenotyping was done. We used immunofluorescence and confocal microscopy.

Results: The Quilty effect was present in 23% of the biopsies, involving 69.7% of the patients without a significant difference between groups (p = 0.509). Rejection was frequently observed in biopsies with the Quilty effect and the effect often recurred in the same patient. Rejection grades 3 to 4 was more frequent in the C group (p = 0.023). There were 5 episodes of Chagas’ disease reactivation with myocarditis in 2 cases. The mean numbers of CD8+ and CD4+ T cells, and the CD4+ to CD8+ ratio were similar for rejection in both groups (p > 0.05), while the CD4+ to CD8+ ratio was significantly lower in chronic C myocarditis compared to rejection in the C group (p = 0.043). There was no significant difference in ischemic damage or interstitial fibrosis in the groups but there was a higher frequency of hypertrophy in the NC group (p = 0.007).

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Conclusions: The histopathological features of heart transplantation in C patients did not differ from that in NC patients in regard to the Quilty effect, development of myocardial fibrosis and ischemia. However, the higher involvement of the C group for rejection grades 3 to 4 suggested higher susceptibility to this event. The similarity of the lymphocytic cellular composition for rejection in both groups indicates that C patients respond to immunological stimulus in a similar pattern as NC patients. J Heart Lung Transplant 2001;20:534–543.

Chagas’ disease is a serious public health problem in Latin America, with approximately 18 million infected individuals and 100 million individuals living in endemic areas.1 Caused by the protozoan Trypanosoma cruzi, the disease is systemic and frequently affects the heart, causing severe cardiac failure and sudden death. The pathogenetic mechanisms involved are complex and have not been fully clarified. The parasite is believed to play a fundamental role during the acute and chronic phases of the disease,2 exerting an immunodepressive effect3, and causing tissue damage by directly acting on infected cells and indirectly by inducing the development of hypersensitivity and autoimmune phenomena.4 In turn, the latter favor the persistence of cardiac inflammation and consequent reparative fibrosis, leading to functional loss of the organ over the years. The absence of effective treatment and the progressive nature of Chagas’ cardiomyopathy has led to alternative therapeutic measures, among which transplantation (Tx) has proved to be promising.5,6 However, considering the systemic nature of the infection with the possibility of reactivation and the constant modulation of the patient immune response by the parasite even after Tx, we questioned whether under these circumstances the response of these patients to transplantation would be similar to that of non-chagasic (NC) heart transplant recipients. In addition, in view of the factors mentioned and under immunosuppressive therapy, the parasite-host interaction may affect the immunological response to the graft, eventually favoring the development of rejection. Works have been published in this area, mainly concerning the clinical aspects.7-12 In this report, we comparatively analyze histopathological findings and the immunohistochemical (IH) profile of the inflammatory infiltrate in endomyocardial biopsies (EMBs) from chagasic (C) and NC heart transplant recipients.

MATERIAL AND METHODS
Population
We studied 33 patients who underwent orthotopic heart transplantation over a period of 5 years. 18 patients were C and 15 NC. NC patients had dilated cardiomyopathy (n = 13), ischemic myocardialopathy (n = 1), and congenital heart disease (n = 1). 22 patients were male (11 C and 11 NC) and 11 were female (7 C and 4 NC) 14 to 63 years old, all of whom had NYHA functional class III or IV heart failure. The donors were serologically tested for Chagas’ disease (hemagglutination and indirect immunofluorescence), syphilis, B and C hepatitis, human immunodeficiency virus, cytomegalovirus, and human T-lymphotropic virus 1 and 2. The investigation was approved by the University Hospital review board and informed consent was obtained from each patient.

Clinico-Surgical Features
The diagnosis of chronic Chagas’ disease was based on epidemiologic data, positive serology (3 samples per patient), as determined by immunofluorescence (IF) and indirect hemagglutination, and on the absence of other cause of cardiomyopathy, such as coronary artery disease, orovavalvular organic disease, alcoholism, or hypertension. In addition, all native hearts of C recipients presented with active myocarditis and with evidence of the parasite in 4 (22%). C patients were eligible for heart transplantation when they presented with refractory congestive heart failure or refractory ventricular arrhythmia after megaesophagus and/or megacolon had been excluded. The surgical procedure was identical in the two groups and was performed as described by Lower and Shumway.13 Patients were treated with triple-drug therapy using cyclosporine, azathioprine and steroids (Table I). The C group received a lower immunosuppression dosage14 because of the risk of reactivating the infection. The diagnosis of reactivation after Tx was based on clinical manifestations, and on the detection of the parasite in blood (xenodiagnosis and culture) and/or in tissue.

Endomyocardial Biopsies
EMBs were performed according to a standard procedure and to the following protocol: weekly
during the 1st month, every 15 days during the 2nd month, and monthly from the 3rd to 6th months with a mean of 4 samples per biopsy. The samples were fixed in 10% buffered formalin, embedded in paraffin and sectioned at 4 μm thickness. A mean of 8 sections per biopsy were stained with hematoxylin and eosin, and Masson’s trichrome.

**Histopathology**

The histopathological examination was performed by one observer (M.M.S.). When necessary, a second observer checked the interpretation of the findings. Endocardial and myocardial changes were evaluated with emphasis on myocarditis (rejection or infection). Acute rejection (AR) was graded according to ISHLT criteria. The presence of myocardial inflammation in the absence of infectious agent was considered to be indicative of allograft rejection. An episode of rejection was defined according to the interval between the first positive EMB and the decrease in the inflammatory infiltrate with changes to a lesser rejection grade or complete resolution of the histological picture on subsequent EMB. Grades 1 to 2 AR that progressed to grades 3 to 4 on subsequent biopsies were considered to be AR episodes indicative of treatment. Subsequent positive biopsies were also regarded as the same episode if not separated by a rejection-free biopsy. Grades 3 to 4 AR were treated with increased immunosuppression or pulsotherapy with methylprednisolone.

EMBs from the C and NC groups with grades 3 to 4 AR and no previous treatment, as well as heart samples from C recipients and post-Tx EMBs with signs of reactivation of C myocarditis, were submitted to IH phenotyping of the lymphocytes in the myocardial inflammatory infiltrate using anti-CD8 and CD4 monoclonal antibodies. The primary antibodies and their dilutions were as follows: CD8 (1:40) (Dakopatts, Denmark) and CD4 (1:20) (Novocastra, United Kingdom). Positive cell counts were performed in all inflammatory fields of the EMBs and in 10 high power fields (×400) with a greater density of the infiltrate in the heart sections from C recipients. Areas adjacent to the endocardium were excluded from analysis. Data are reported as the mean number of positive cells per high power field of the inflammatory infiltrate.

A search for *T. cruzi* was performed in all EMBs from the C group for which lymphocyte immunophenotyping was done. Double labeled anti-*T. cruzi* 4B9 and 2C2 monoclonal antibodies were used in the indirect IF technique and readings were taken with a confocal microscope. The presence in the endocardium of the Quilty effect was analyzed in terms of frequency, time of appearance, and histological type.

In addition, interstitial fibrosis and myocyte hypertrophy were semiquantified in each EMB and graded from 0 to 3+, corresponding to absence, and mild, moderate and marked presence. Myocyte hypertrophy was assessed based on nuclear alterations, including enlargement, hyperchromicity, and irregular borders, according to Edwards. The presence of ischemic changes and vascular changes, such as endothelial swelling and vasculitis, were evaluated.

### TABLE I

<table>
<thead>
<tr>
<th>Period</th>
<th>Immunosuppressive drugs</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>NC</td>
</tr>
<tr>
<td>Before operation</td>
<td>Azathioprine*</td>
<td>Same</td>
</tr>
<tr>
<td>Intra-operation</td>
<td>Methylprednisolone**</td>
<td>Same</td>
</tr>
<tr>
<td>Post-operation (P.O.)</td>
<td>Azathioprine</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>Maintain after 2nd month</td>
</tr>
<tr>
<td></td>
<td>0.8–1 mg/kg/g (4th P.O. day tapered) until 1st month followed by 0.15–0.20 mg/kg/g (until 2nd month)</td>
<td></td>
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<tr>
<td></td>
<td>Cyclosporine***</td>
<td>4.4–6.1 mg/kg/day, mean 4.6 mg (4th P.O. day) 5.3 mg (4th P.O. day)</td>
</tr>
</tbody>
</table>

*Adjusted to maintain a white blood cell count of less than 3,000/mm.³.
**After removal of the aortic cross clamp.
***Dosage adjusted to maintain serum levels around 200 mcg/L.
Statistical Analysis
Qualitative variables were analyzed statistically by the Pearson chi-square test. Fisher’s exact test was applied when there were expected frequencies less than 5. Quantitative variables were compared using the Mann-Whitney test except for age, in which Student’s test was applied. Normal distribution was tested by the Kolmogorov-Smirnov test. Kaplan-Meier curves for event-free time were calculated for rejection and the Quilty effect. The log rank test was used to compare the curves using the SPSS: Statistical Package for Social Science (SAS Institute, Cary, NC).

RESULTS
General Findings
In both groups there was a predominance of male patients (61.1% in the C and 73.3% in the NC group), with a similar distribution in both groups (p = 0.458). Moreover, there was no difference in the C and NC groups concerning patient age (mean age 37.6 years in the C group and 41.4 in the NC group, p = 0.238).

Endomyocardial Biopsies
A total of 293 EMBs were analyzed, with a mean of 9 biopsies per patient (range 1 to 16).

The Quilty effect.
This change was present in 23% of the EMBs, involving 69.7% of the patients. Although the lesion was observed earlier and more frequently in the NC group, in which 7 of the 11 patients presented with the first positive biopsy within the first post-Tx month, there was no significant difference between the groups (log rank test p = 0.509). Both groups showed recurrence of the lesion in subsequent biopsies in the same patient. Signs of rejection were frequently observed in EMBs with the Quilty effect. The two lesions occurred together in 61.2% of biopsies (18 in the C and 23 in the NC group) in a total of 67 EMBs with the Quilty effect. On the other hand, when we considered only rejection grades 3 to 4, this occurred in lower proportion (20 EMBs). Another aspect related to rejection was that the Quilty effect preceded an episode of rejection in only 15% of EMBs. There was a predominance of type A lesions in both groups, for a total of 43 from 67 EMBs with the Quilty effect.

Endocardial fibrosis and thrombosis predominantly occurred at a previous biopsy site, a phenomenon observed in 37.8% of the samples.

Rejection.
Of the EMBs 42.3% showed signs of rejection. The number of episodes per patient was similar in the two groups, including 1.8 for C and 1.6 for NC (p = 0.614), regardless of grade, over a mean histological follow-up of 241 days for the C and 210 days for the NC group. On the other hand, for grades 3 to 4 AR, the number of episodes as well as the number of patients with this type of rejection were higher in the C group (p = 0.033 and 0.027, respectively). The Kaplan-Meyer curves showed a significant difference between the groups (Figure 1). Actuarial freedom from grades 3 to 4 AR during the 1st, 3rd and 6th months of follow-up was 67%, 50%, and 22% for the C group, and 93%, 80%, and 60% for the NC group. The mean linearized rate of treated rejection episodes (grades 3 to 4) for the first 6 months of follow-up was 0.15 ± 0.10 episodes per month per patient in the C group and 0.08 ± 0.11 in the NC group (p = 0.044).

For both groups, rejections occurred mainly during the first 2 months of follow-up, especially in the first two weeks (66% of cases). The new AR episodes in patients who had rejection during the first weeks of follow-up were frequently of higher intensity.

The IH characterization of the myocardial inflammatory infiltrate revealed a predominance of T CD8+ cells in the episodes of rejection in the C and NC groups, and in the reactivation of C myocarditis. The mean number of T CD8+ cells in EMBs with rejection in the C and NC groups was 2.52 and 2.38, while the mean number of T CD4+ cells was 2.10 and 1.52, with a T CD4+-to-CD8+ ratio of 0.80 and 0.63, respectively. There was no significant difference in the mean numbers of CD8+ and CD4+ T cells or the CD4+-to-CD8+ ratio between the C and NC groups (Table II, Figure 2). On the other hand, the T CD4+-to-CD8+ ratio was significantly lower in the C group before Tx (chronic C myocarditis) compared to the C group after Tx (rejection) (Table III). The values of CD4+, CD8+, and the CD4+-to-CD8+ ratio in the reactivation of C myocarditis were 2.52, 2.86 and 0.88, respectively.

Vessels.
Vasculitis was detected in only two biopsies, both in the C group. One case occurred simultaneously with intense cell rejection, which caused patient death. In both groups, allograft chronic vasculopathy was not detected during the study period. Signs of endothelial activation was more frequently observed in the EMBs of the C group.
Reactivation.
The reactivation of Chagas' disease occurred in 4 patients with 5 episodes clinically manifesting as fever, cutaneous nodules, and myocarditis ($n = 2$), which were successfully treated with allopurinol. One episode occurred after the treatment of acute rejection. EMBs with myocarditis revealed parasites in 2 cases by light microscopy and indirect IF (Figure 3).

Ischemia.
Ischemic damage occurred at a similar proportion in both groups, including in 11 patients in the C group and 9 in the NC group ($p > 0.999$), usually during the first two weeks post-Tx.

Hypertrophy and interstitial fibrosis.
The number of patients with one or more EMBs presenting with myocyte hypertrophy was 16 in the C and 13 in the NC group, with a significantly higher involvement in the EMBs of the NC group ($p = 0.007$). Interstitial fibrosis did not differ significantly in frequency or intensity between the groups ($p = 0.240$ and 0.234, respectively). The mean number of EMBs with fibrosis per patient was 3.1 and 2.4 in the C and NC groups, respectively.

**DISCUSSION**
Chagas' disease, particularly its pathogenesis, has been the subject of many investigations. Cardiac involvement frequently causes severe cardiac failure with a poorer prognosis compared to cardiomyopathy of other etiologies.$^{18}$ Recently, heart transplantation has become a good therapeutic option for terminal patients, despite the possibility of recurrent infectious disease.$^{5, 6}$

Experience accumulated over the years has led to improved survival, stimulating the increasing number

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**TABLE II** Mean numbers of CD4+ and CD8+ T cells, and CD4+-to-CD8+ ratio in the C and NC heart transplant recipients with EMBs analyzed with acute rejection

<table>
<thead>
<tr>
<th>Group</th>
<th>CD4+</th>
<th>CD8+</th>
<th>CD4+-to-CD8+ Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>2.10</td>
<td>2.52</td>
<td>0.80</td>
</tr>
<tr>
<td>NC</td>
<td>1.52</td>
<td>2.38</td>
<td>0.63</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.18</td>
<td>0.34</td>
<td>0.57</td>
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</table>
of heart transplants in these patients. Consequently, the study of the complex mechanisms involved in the parasite-host interaction after Tx is of special interest and was the focal point of the present study.

The Quilty Effect

Quilty lesions are frequently observed in EMBs after heart Tx. Predominantly consisting of T lymphocytes, these lesions persist without a defined cause. The incidence of this phenomenon is variable, with rates ranging from 5% to 13% of EMBs and 49.7% to 78.6% of patients. As observed by others authors, this endocardial alteration was common in our series and recurred frequently in the same patient. This aspect has been attributed to a probable genetic predisposition or individual sensitivity to cyclosporine. The nature of native cardiopathy may be related to a higher frequency of Quilty lesion after Tx, as observed in dilated cardiomyopathy compared with ischemic cardiomyopathy. In our series, the presence of Quilty lesions showed a tendency to be more frequent and an earlier event in the NC group, in accordance with previous report that related frequency and time for the first occurrence to the Quilty effect. Our data

<table>
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<tr>
<th>TABLE III</th>
<th>Mean number of CD4+ and CD8+ T cells, and CD4+-to-CD8+ ratio in the C myocarditis group before and after heart Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C group</td>
</tr>
<tr>
<td>Before Tx</td>
<td>13.37</td>
</tr>
<tr>
<td>After Tx</td>
<td>2.10</td>
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</table>

*p = 0.043.
suggested no correlation between the Quilty effect and rejection grade, which reinforced the belief that the Quilty effect has little value for predicting rejection.21,22

Rejection

Despite improvements in immunosuppressive therapy, AR is still one of the most important causes of death after Tx.24 Regardless of grade, the chronology of the rejection episodes in our series was as expected, with most rejections occurring within the first 2 months after Tx.25 Early occurrence of the event was related to higher rejection grades in subsequent episodes.

Different from other reports,7,12 in our sample treated AR (grades 3 to 4) was more frequently observed in the C group, which suggested higher susceptibility of this group to rejection. The attempt to maintain immunosuppression at a lower range, even within therapeutic limits, may have favored rejection in this group. On the other hand, Almeida14 and Bocchi et al12 studied C patients post-Tx and did not find a difference in the number of treated rejection episodes in those using lower doses of immunosuppression compared with those using habitual dosages. They reported similar successful heart transplantation follow-ups in C and NC patients. In contrast, others have observed a lower incidence and severity of AR in C patients compared to NC patients, and suggested that this finding probably results from or is related to the depletion of CD4+ cells promoted by the parasite.7 Accordingly, we confirmed a lower number of CD4+ cells in native C heart recipients compared with AR in NC patients, as previously documented. However, the ratio of CD4-to-CD8 cells in the same C patients post Tx did not differ from that in NC patients, which suggested that they are as able to respond to the immunological stimulus as NC patients.

As previously reported, the occurrence of myocarditis before Tx favors the development of early, more severe, and more frequent rejection episodes, which has been attributed to hyperactivity of the immune system in these patients.26,27 This phenomenon may have represented an additional risk factor for rejection in the C group.

In addition, morphological signs of endothelial activation in the microvasculature, as previously described,28 were more frequently observed in the C group. At least two factors may have contributed to the vascular alterations, including the immune response against the graft that was triggered by rejection and the presence of the parasite in the host, causing a systemic endothelial response.29,30

In C transplant recipients, when the equilibrium between a quiescent infection and host defenses is broken, Chagas’ disease is often reactivated in the form of myocarditis that is histologically indistinguishable from rejection. This is an important and crucial point in C heart Tx in regard to therapy. Actually, only the identification of the agent and/or its antigens by IH, IF or T. cruzi-specific polymerase chain reaction permits separation of the two processes. An adequate clinico-morphological correlation, especially with the level of immunosuppression, helps to select treatment. Moreover, the aggressive therapy for AR may open the way to Chagas’ reactivation that does not always present at EMB. Surprisingly, most reactivation episodes have a good response to treatment. This favorable course has encouraged heart Tx in C patients.12 In summary, the intensity of parasitism, which is related to a deficient immunological response,2 and the grade of myocardial damage determine the outcome of a reactivation episode.

To clarify the complex pathogenesis of Chagas’ disease, important advances have been achieved,
especially in the field of immunology. It has been established that during the acute phase of Chagas’ disease, the parasite alters the immune system of the host, triggering immunodepression that favors its installation and dissemination. In vitro, the parasite induces a lower expression of CD3, CD4, CD8, and interleukin-2r surface molecules in activated lymphocytes, which causes the impairment, not only of the T-lymphocyte subpopulations, but also of the function of other interconnected cells. However, the occurrence of an immunodepressive stage during the chronic phase is controversial. In some experimental and human studies, a lower level of CD4+ T cells has been observed by IH investigation of the cellular composition and cytokines produced at the inflammatory sites of affected tissues, while in others, a predominance of CD4+ T cells has been reported. On the other hand, it has been shown in an experimental model that strains with different biological behaviors, such as virulence and tropism, cause tissue injury through different types of T-lymphocyte subtypes, a fact that indicates the importance of the parasite in the development of different mechanisms of muscular and neuronal damage.

In contrast to the pre-Tx phase, in which we confirmed a lower CD4+-to-CD8+ tissue ratio in C group patients, after heart Tx the number of CD4+ T cells increased, as in AR, and reactivation episodes were similar to those observed in AR of the NC group.

Tarleton et al. have recently studied the cell composition of the myocardial inflammatory infiltrate in transplanted hearts and compared it to that of the native heart in mice chronically infected with T cruzi. Similar to our finding, they showed that the inflammatory response in terms of the cell types present was different in the native hearts of T cruzi-infected mice and allogeneic heart rejection, the latter with a higher number of CD4+ T cells.

Potential organ donors in Chagas’ disease endemic areas are tested for Chagas’ disease. Organs retrieved from a Chagas’ disease-positive donors are not transplanted into Chagas’ disease-negative recipient. In addition, no other organ transplants but the heart in C patients are usually performed. Therefore, there are very few published data on the possible outcome of these transplants that compare findings with those of heart transplantation in C patients.

Fibrosis, Hypertrophy, and Ischemia

In the long term, transplanted hearts are subject to myocardial fibrosis and hypertrophy. Interstitial fibrosis may be demonstrated in the initial phases of Tx, with no relationship to hemodynamic abnormalities, and it is usually detected in patients treated with cyclosporine and prednisone. The value of this finding in EMBs is relative, with doubts about the effects that it may have on the graft. Among related factors are the use of cyclosporine, prolonged ischemia time, and rejection, although there is no consensus among authors. Despite differentiated immunosuppressive treatment, the number of EMBs with fibrosis and the intensity of the alterations were similar in both groups.

On the other hand, myocyte hypertrophy was observed more frequently in the NC group. We found no satisfactory explanation for this finding, since the mean number of EMBs obtained, the time of evolution, and the intensity of myocardial fibrosis were similar in the two groups. Factors reported to promote post-Tx hypertrophy are systemic arterial hypertension, which favors the development of myocardial fibrosis, hemodynamic disorders related to the use of cyclosporine, denervation of the transplanted heart, and increased pulmonary arterial pressure. However, none of these factors was considered important by the clinical registry. Further investigations are necessary to confirm our findings.

The major cause of ischemic injury is a prolonged period of ischemia of the donor heart. Lower post-Tx survival has been related to the development of fibrosis and atherosclerosis after transplantation. The lesion usually occurs during the initial phases of Tx. During late phases, it results from deficient perfusion due to vascular disease in the graft. The incidence in newly transplanted patients is variable. We observed no difference in the behavior of the C and NC groups in this respect. Alterations always occurred during the early phases of Tx and did not correlate with patient survival, as reported by others.

In summary, based on our histopathological findings in a relatively small number of patients, we conclude that C patients submitted to heart Tx did not differ from NC patients in many aspects, such as the incidence of the Quilty effect, the development of myocardial fibrosis, and ischemia. However, the behavior of the C group suggested higher susceptibility to rejection that may be related to myocarditis before Tx or to problems with immunosuppressive therapy for controlling the rejection and reactivation of Chagas’ disease. The composition of inflammatory infiltrate in rejection was similar in both groups of patients but differed from that observed in chronic C myocarditis pre-Tx, suggesting that, de-
spite immunomodulation exerted by the parasite, C group patients respond in a similar pattern to immunological stimulus. Furthermore, the similarity of the subsets of lymphocytes in the myocardial infiltrate became indistinguishable in terms of process, rejection and C myocarditis reactivation. Otherwise, further studies are necessary to clarify the apparent change in the pattern of C myocarditis pre-TX and post-Tx, as well as the inexplicable higher involvement in NC group EMBs by myocyte hypertrophy.

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