Pathology of Chronic Chagas Cardiomyopathy in the United States

A Detailed Review of 13 Cardiectomy Cases

Evan P. Kransdorf, MD, PhD, Mike C. Fishbein, MD, Lawrence S. C. Czer, MD, Jignesh K. Patel, MD, PhD, Angela Velleca, RN, CCTC, Henry D. Tazelaar, MD, R. Raina Roy, MD, D. Eric Steidley, MD, Jon A. Kobashigawa, MD, and Daniel J. Luthringer, MD

From the Division of Cardiovascular Diseases and Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona, Scottsdale, AZ; Department of Pathology and Laboratory Medicine, University of California Los Angeles, Los Angeles, CA; Cedars-Sinai Heart Institute, Los Angeles, CA; Department of Cardiology, Maricopa Integrated Health System, Phoenix, AZ; and Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA.

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ABSTRACT

Objectives: The pathologic features of chronic Chagas cardiomyopathy may not be widely appreciated in the United States. We sought to describe the gross, microscopic, immunohistochemical, and molecular pathology features useful to diagnose chronic Chagas cardiomyopathy.

Methods: The features from a case series of cardiectomy specimens of patients undergoing heart transplantation (12 patients) or mechanical circulatory support device implantation (one patient) for chronic Chagas cardiomyopathy at three institutions in the United States are reported and analyzed.

Results: Gross findings included enlarged and dilated ventricles (100% of cases), mural thrombi (54%), epicardial plaques (42%), and left ventricular aneurysm (36%). Microscopic evaluation revealed myocarditis (100% of cases) characterized by mononuclear cell infiltration, fibrosis (100%), nonnecrotizing granulomas (62%), and giant cells (38%). Two specimens (15%) showed rare intracellular amastigotes. Immunohistochemical assays for Trypanosoma cruzi organisms were negative in all cardiectomy specimens, whereas tissue polymerase chain reaction was positive in six (54%) of 11 cases.

Conclusions: The gross and microscopic features of chronic Chagas cardiomyopathy in the United States appear similar to those reported in endemic countries. Importantly, tissue polymerase chain reaction may be useful to confirm the diagnosis.

Chagas disease is caused by infection with the parasite Trypanosoma cruzi (TC). TC has been deemed a “neglected tropic disease” by the World Health Organization and is a major cause of morbidity and mortality in Central and South America. Worldwide immigration patterns have led to significant populations of persons with chronic TC infection outside of endemic countries, with reports of 300,000 affected individuals in the United States. Chagas cardiomyopathy (CC) is a manifestation of chronic infection that occurs in up to 30% of untreated patients and commonly results in end-stage heart failure. Heart transplantation remains the optimal therapy for patients with CC, after which recipients experience posttransplant survival rates comparable to other indications. Reactivation of the infection after transplant is a serious complication that can lead to allograft failure and death.

Nonfamiliarity with the epidemiologic, clinical, and pathologic features of CC in both organ donors and recipients in the United States has led to adverse outcomes. Knowledge of Chagas disease and the pathologic features related to CC are essential for diagnosis and subsequent clinical and laboratory monitoring for potential TC reactivation posttransplant.

The pathology of chronic CC has been studied for more than 50 years. Features of CC include biatrial and biventricular dilation, mural thrombi, left ventricular aneurysm formation, and epicardial fibrosis. Microscopic findings typically include fibrosis with diffuse inflammatory infiltrates. Recently, high-grade myocarditis has been associated with TC persistence posttransplantation.

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Although the presence of intracellular amastigotes is considered the diagnostic hallmark, they are present in only a minority of cases. Thus, the absence of the TC organisms can make the tissue diagnosis challenging. Application of immunohistochemical and molecular techniques, specifically polymerase chain reaction (PCR) for TC gene products, is thought to be a more sensitive marker of TC organism persistence.

Importantly, patients with end-stage heart failure due to CC in the United States are likely to survive longer than in endemic countries due to differences in management, such as high utilization of implantable cardioverter defibrillators, cardiac resynchronization therapy, and ventricular assist devices. Indeed, the average age at the time of heart transplant appears to be higher in patients undergoing heart transplant in the United States than in Brazil. As such, the pathologic features of CC in cardiectomy specimens in the United States might be expected to be more severe, with a higher prevalence of left ventricular aneurysm formation or T. cruzi amastigotes, for example, than classic findings described in endemic countries.

This study was undertaken to evaluate the pathologic features of chronic CC in a US-derived cohort of patients. The intent was multifold. First, we sought to identify differences in the pathology of our US cohort vs the classically described findings of CC from endemic regions. We also strived to reiterate the pathologic features of CC to facilitate recognition of CC. Finally, we analyzed the potential utility of immuno-histochemical and tissue-based PCR to aid in diagnosing myocardial involvement by TC organisms in this population.

Materials and Methods

Study Population

We performed a retrospective review of all patients undergoing implantation of a mechanical circulatory support device or heart transplant at Cedars-Sinai Medical Center, University of California Los Angeles Medical Centers, and Mayo Clinic Arizona between 2006 and 2013. Clinical data abstracted from the medical record included age, sex, country of birth, treatment (heart transplant or total artificial heart), and method of diagnosis of TC (serology or on endomyocardial biopsy). Patients were diagnosed with CC if serum samples tested positive for antibodies to TC at any point in their clinical course or pathologic specimens showed T. cruzi amastigotes. This study was performed under an approved protocol of the Cedars-Sinai Medical Center (institutional review board [IRB] 22311) and Mayo Clinic Arizona Institutional Review Boards (IRB 14-008587). All original glass slides, gross photos, and associated reports from the explanted hearts and any relevant posttransplant biopsy specimens were reviewed.

Gross Examination of Explanted Hearts

Explanted cardiac tissue was examined macroscopically in a systematic manner based on established gross examination protocols. Features evaluated included specimen weight, chamber enlargement/dilation, myocardial and epicardial scarring, mural thrombi, aneurysm formation, and epicardial plaques. All tissues were fixed in 10% formalin. Predicted heart weight by body surface area was taken from regression equations derived from 384 autopsy cases.

Histopathology

Representative tissue sections were submitted by standard protocols, which included sampling from the left and right ventricles, septum, and all grossly identified lesions. The 4-μm-thick sections were cut from paraffin blocks and stained with H&E. Features evaluated and graded semiquantitatively (scale 0-3) included the cellular infiltrate, fibrosis, granulomas, necrosis, and giant cells. Relevant posttransplant endomyocardial biopsy specimens were similarly reviewed.

Immunohistochemistry and PCR Analysis

Special testing was performed at the Infectious Disease Pathology Branch of the Centers for Disease Control and Prevention. Immunohistochemical assays used an immunooalkaline phosphatase technique with a polyclonal rabbit anti-TC antibody diluted at 1/5,000 on 4-μm-thick sections derived from paraffin blocks. PCR was performed (“tissue PCR”) by extracting DNA from formalin-fixed, paraffin-embedded tissue sections and then applying the PCR assays for TC. This multitarget PCR assay uses three targets (kineto plast DNA [kDNA], TCZ, and 18S ribosomal RNA); a specimen that tests positive for all three targets is reported as positive, whereas a specimen that is positive only for the kDNA or TCZ targets is reported as indeterminate.

Results

Clinical Parameters

Thirteen cases of chronic CC were identified. All patients originated from Chagas-endemic countries. The age range at the time of explantation was 37 to 69 years with eight (62%) women and five (38%) men. Twelve underwent cardiectomy for heart transplant (12/13, 92%) and one for total artificial heart implantation. Eleven of 13 patients were diagnosed with chronic CC by serology prior to surgery. Two patients (patients 1 and 8) were serologically indeterminate.
prior to surgery and were subsequently diagnosed posttransplant with acute TC reactivation by TC seroconversion (patient 1) or observation of TC amastigotes in endomyocardial biopsy specimens (patient 8).

Summary of Gross Pathology Features
Cardiectomy mass exceeded heart mass predicted from patient body surface area in 10 (83%) of 12 cases Image 1. The mean percentage of actual to predicted heart weight was 122% (mean for men 133%, mean for women 115%), consistent with hypertrophy of the left and right ventricles. The gross pathology features of the 13 explanted hearts are detailed in Table 3. Atria could not be adequately examined due to the method of surgical resection. Four explants exhibited aneurysms of the left ventricular apex. Seven explants had mural thrombi involving the left ventricle, three of which were found in apical aneurysms. Five explants demonstrated epicardial plaques, all of which involved the anterior wall of the heart.

Summary of Microscopic Pathology Features
Microscopic evaluation showed myocarditis in all 13 (100%) cases, characterized by mononuclear cell infiltration Image 2 composed of varying numbers of lymphocytes, plasma cells, histiocytes, and eosinophils. Cases were descriptively classified as “eosinophilic” myocarditis Table 4. Neutrophils were not a common feature. All cases showed varying degrees of interstitial fibrosis, usually found in a

| Table 1 |
| Clinical Parameters of Patients With Chronic Chagas Cardiomyopathy |
| Patient No. | Sex | Country of Birth | Age, y | Therapy | Method of TC Diagnosis |
|------------|-----|------------------|--------|---------|------------------------|
| 1          | M   | El Salvador      | 57     | HT      | Posttransplant serology |
| 2          | F   | El Salvador      | 62     | HT      | Serology               |
| 3          | M   | Mexico           | 69     | HT      | Serology               |
| 4          | F   | El Salvador      | 52     | HT      | Serology               |
| 5          | M   | Mexico           | 56     | HT      | Serology               |
| 6          | F   | El Salvador      | 54     | HT      | Serology               |
| 7          | F   | Mexico           | 50     | HT      | Serology               |
| 8          | M   | Belize           | 37     | HT      | Posttransplant EMBx    |
| 9          | M   | Mexico           | 62     | HT      | Serology               |
| 10         | F   | El Salvador      | 52     | HT      | Serology               |
| 11         | F   | El Salvador      | 53     | TAH     | Serology               |
| 12         | F   | El Salvador      | 58     | HT      | Serology               |
| 13         | F   | Honduras         | 54     | HT      | Serology               |

EMBs, endomyocardial biopsy; HT, heart transplant; TAH, total artificial heart; TC, Trypanosoma cruzi.

| Table 2 |
| Ventricular Mass of Cardiectomy Specimens With Chronic Chagas Cardiomyopathy |
| Patient No. | Cardiectomy Weight, g | Body Surface Area, m² | Predicted Heart Weight, g | Actual to Predicted Heart Weight, % |
|-------------|------------------------|------------------------|---------------------------|-----------------------------------|
| 1           | 450                    | 1.7                    | 344                       | 131                               |
| 2           | 395                    | 1.5                    | 301                       | 131                               |
| 3           | 410                    | 1.6                    | 314                       | 131                               |
| 4           | 260                    | 1.6                    | 305                       | 85                                |
| 5           | 565                    | 1.9                    | 371                       | 152                               |
| 6           | 332                    | 1.5                    | 289                       | 115                               |
| 7           | 433                    | 1.4                    | 273                       | 159                               |
| 8           | 382                    | 1.8                    | 370                       | 103                               |
| 9           | 483                    | 1.6                    | 325                       | 149                               |
| 10          | 276                    | 1.4                    | 273                       | 101                               |
| 11          | 288                    | 1.7                    | 331                       | 87                                |
| 12          | 394                    | NA                     | NA                        | NA                                |
| 13          | 323                    | 1.3                    | 260                       | 124                               |

NA, data not available.

| Table 3 |
| Select Gross Pathologic Features of Chronic Chagas Cardiomyopathy |
| Patient No. | Left Ventricular Aneurysm | Mural Thrombi | Epicardial Fibrous Plaques |
|-------------|---------------------------|---------------|---------------------------|
| 1           | –                         | +             | Unknown                   |
| 2           | –                         | –             | –                         |
| 3           | –                         | +             | –                         |
| 4           | –                         | +             | –                         |
| 5           | +                         | +             | –                         |
| 6           | +                         | +             | –                         |
| 7           | –                         | –             | –                         |
| 8           | –                         | –             | +                         |
| 9           | –                         | –             | +                         |
| 10          | Unknown                   | –             | +                         |
| 11          | +                         | +             | –                         |
| 12          | Unknown                   | +             | –                         |
| 13          | +                         | –             | –                         |
| Total       | 4/11                      | 7/13          | 5/12                      |

+, positive; –, negative.

| Table 4 |
| Select Histopathologic, Immunohistochemical, and Molecular Features of Chronic Chagas Cardiomyopathy |
| Patient No. | Giant Cells | Granulomas | Trypanosoma cruzi Identification |
|-------------|-------------|------------|---------------------------------|
|             | Microscopy  | Tissue IHC | Tissue PCR                      |
| 1           | –           | –          | Indet                           |
| 2           | +           | +          | +                               |
| 3           | –           | –          | –                               |
| 4           | +           | +          | +                               |
| 5           | –           | –          | –                               |
| 6           | –           | –          | –                               |
| 7           | –           | –          | –                               |
| 8           | –           | +          | +                               |
| 9           | +           | –          | +                               |
| 10          | –           | –          | NP                             |
| 11          | +           | –          | +                               |
| 12          | +           | +          | NP                             |
| 13          | +           | +          | +                               |
| Total       | 5/13        | 8/13       | 0/12                           |

IHC, immunohistochemistry; Indet, indeterminate; NP, not performed; PCR, polymerase chain reaction; +, positive; –, negative.
patchy distribution throughout the myocardium, subendocardium, and epicardium of both ventricles and septum. Eight cases contained nonnecrotizing granulomas associated with a few degenerating myocardial fibers but no necrosis. Five cases showed the presence of multinucleated giant cells, almost always in the context of granulomas. Two explant cases showed rare intracellular parasitic organisms (amastigote forms) within myocardial fibers. One posttransplant endomyocardial biopsy specimen from patient 8 showed intracytoplasmic cysts containing organisms 5 μm in size, with cell membranes, small nuclei, and tiny intracytoplasmic condensations (corresponding to a kinetoplast), features that are unique to TC and distinct from fungal forms such as *Histoplasma*. Also noted were myofiber degeneration, edema, and few lymphocytes (Image 2F), which led to the diagnosis of acute reactivation of Chagas disease in this particular case.

**Summary of Immunohistochemical and Molecular Pathology Features**

Immunohistochemical analysis (Table 4) was negative for TC antigens in all 12 explant specimens tested. Tissue PCR analysis proved positive for TC probes in six (55.6%), negative in three (33.3%), and inconclusive in two of 11 cases tested. One posttransplant biopsy specimen and

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**Image 1** Gross photographs of explanted Chagas cardiomyopathy hearts. Representative examples of explanted hearts with (A) cardiomegaly due to multichamber dilation. B. Cardiomegaly due to multichamber dilation. Epicardial fibrous plaques are also noted. C. Cross section of cardectomy specimen highlighting left ventricular myocardial scarring, primarily involving the anterior wall, with aneurysm formation. D. Left ventricular apical aneurysm with variable myocardial scarring and endocardial thrombus.
Autopsy myocardium of patient 8, with acute reactivation of Chagas disease, stained positive with the immunochemical assay (Image 2H) and reacted positively with the tissue PCR assay.

Discussion

The classic pathologic features of chronic CC have been well documented in studies from endemic areas.\textsuperscript{9,19-21} In our cohort of US-derived cases, gross changes consistently included biventricular dilation and hypertrophy, as well as varying degrees of myocardial and epicardial fibrosis/scarring. Four cases had left ventricular aneurysms, seven had mural thrombi, and five had epicardial plaques. Left ventricular aneurysms are not common but are seen in certain types of cardiomyopathy, for example, in hypertrophic and ischemic cardiomyopathies. In hypertrophic cardiomyopathy, an incidence of 2\% has been reported,\textsuperscript{22} whereas in ischemic cardiomyopathy resulting from myocardial infarction, an incidence of 20\% has been reported.\textsuperscript{23,24} Left ventricular thrombi have been identified in around 5\% of patients with dilated cardiomyopathy. Thus, the presence of a left ventricular aneurysm or a left

\textbf{Image 2} Photomicrographs of cardiac tissue affected by Chagas cardiomyopathy. Representative photomicrographs of cardiac tissue affected by Chagas disease. \textbf{A}, Nonnecrotizing granuloma admixed with mixed mononuclear cells, including lymphocytes, plasma cells, histiocytes, and few eosinophils (×200). \textbf{B}, Higher magnification showing numerous lymphocytes, plasma cells, and histiocytes (×400). \textbf{C}, Mixed mononuclear cells, including many eosinophils (×400). \textbf{D}, Significant interstitial fibrosis/scarring without mononuclear cells (×200).
ventricular thrombus is not specific to the diagnosis of CC. In contrast, epicardial plaques (also known as “milk spots”) are very rare and have most commonly been reported in the setting of CC.20

At the microscopic level, the inflammatory myocarditis of classic CC has been described as predominantly lymphocytic,11 lymphomononuclear,25 polymorphic with eosinophils,26 and granulomatous.9 In our series, all cases showed these features of mixed lymphoplasmacytic infiltrates, and all had varying numbers of eosinophils. Granulomas were found in more than half of the cases, and multinucleated giant cells were also found in around 40% of cases. Molina and Kierszenbaum26 found that eosinophilic infiltration was highest in areas of necrosis. We were not able to verify this observation, since necrosis was not seen in any of our cases. The nature and significance of the pattern of inflammatory cell infiltrate remain unclear but have been linked to patient-specific variation in cytokine expression.27

Intracytoplasmic amastigote forms were found in only 15% of our cases. This is in agreement with the literature, where most studies have failed to identify TC amastigotes in tissue from patients with chronic CC.11,25 Thus, in the context of a diagnostic heart biopsy, cardiac resection, or autopsy in a patient with unspecified heart failure or cardiomyopathy, it is
important to note that in the absence of intracellular TC organisms, the differential diagnosis for this pattern of myocarditis, especially in the presence of granulomas and multinucleated giant cells, could be very broad, including such etiologies as drug reaction, autoimmune and giant cell myocarditis, sarcoidosis, and other infectious agents.

Alternative methods, including immunohistochemical and tissue-based PCR assays, have been employed to enhance tissue detection of the TC organisms. Previous studies using immunohistochemical assays in endemic countries have been mixed, with one study showing frequent observation of TC amastigotes and another failing to observe TC amastigotes. In our series, application of an immunohistochemical assay to potentially enhance the detection of TC in tissue sections was not useful. The analysis included two cases with morphologically evident organisms (explant case 10 and the posttransplant reactivation biopsy with subsequent autopsy of case 8). The explant case 10 was negative by immunohistochemical assay, as the rare organisms were not present on the level used for the immunohistochemical study. Following reactivation of TC posttransplant in case 8, numerous TC amastigote forms could be easily seen on the biopsy specimen and autopsy, and both samples were strongly reactive in the immunohistochemical assay. However, using a tissue-based PCR assay, Benvenuti et al recently showed that 60% of tissue specimens in their series of 30 yielded positive PCR, with a higher percentage positive in patients with TC reactivation compared with those without reactivation, although the difference between the groups was not statistically significant. In our series, six of 11 cases evaluated were positive using the tissue-based PCR assay, giving a detection sensitivity of 55%.

Conclusions

In summary, we have shown that the gross and microscopic features of chronic CC in patients undergoing mechanical circulatory support device implantation or heart transplant in the United States are generally similar to the classic features reported in endemic countries. One exception is the absence of necrosis in our cohort, which Molina and Kierszenbaum identified in three of 10 CC cases in Argentina. Furthermore, tissue-based PCR assays are useful to confirm the diagnosis of CC but have only modest sensitivity. It is hoped that increased awareness of these pathologic features will allow pathologists to maintain vigilance for Chagas disease as an important etiology of myocarditis and end-stage cardiomyopathy in the United States. Since pathologists frequently do not know a patient’s country of origin, the finding of myocarditis with the above features should prompt a discussion with the patient’s clinicians about the differential diagnosis and potential utility of ordering appropriate serologic and pathologic testing.

Corresponding author: Evan P. Kransdorf, MD, PhD, Cedars-Sinai Heart Institute, 8336 Wilshire Blvd, #301, Beverly Hills, CA 90211; evan.kransdorf@cshs.org.

*Dr Kransdorf is currently with the Cedars-Sinai Heart Institute, Los Angeles, CA.

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