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# *Severe and rapidly progressive heart failure in a young adult patient with chronic chagas cardiomyopathy: diagnostic and therapeutic challenge*

# *Insuficiência cardíaca grave e rapidamente progressiva em paciente adulto jovem com cardiomiopatia chagásica crônica: desafio diagnóstico e terapêutico*

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Morais AFP, Souza DFS, Tomazini MHF, Bachur CK, Oliveira RPC. Severe and rapidly progressive heart failure in a young adult patient with chronic chagas cardiomyopathy: diagnostic and therapeutic challenge / *Insuficiência cardíaca grave e rapidamente progressiva em paciente adulto jovem com cardiomiopatia chagásica crônica: desafio diagnóstico e terapêutico*. Rev Med (São Paulo). 2020 Sept-Oct;99(5):512-8.

**ABSTRACT**: Chagas disease is responsible for 12 thousand deaths annually in the Americas, mainly due to Chronic Chagas Cardiomyopathy (CCC) that occurs in 20 to 30% of those infected people, after 60 years old, 30 to 40 years after the first infection, leading to biventricular heart failure (HF), arrhythmias, blocks and embolisms. The diagnosis is based on epidemiology, clinical condition, electrocardiographic changes and imaging tests associated with serology. The present study reports the case of a patient with atypical evolution for her age due to rapid progression to advanced and refractory HF, associated with high morbidity and mortality, a typically late manifestation of CCC. Clinical case: 37 years old female patient admitted to the Intensive Care Unit of a tertiary hospital in a city of São Paulo State for decompensated congestive heart failure, associated with pleural effusion. The echocardiogram and serology for *Trypanosoma Cruzi* confirmed the diagnosis of CCC and risk of mortality estimated in 84%. Treatment started with beta-blocker, spironolactone, diuretic, enalapril and patient was discharged from hospital. After 20 months, she was readmitted with cardiogenic shock, cardio-renal syndrome and atrial fibrillation treated with diuretics, inotropic and amiodarone, and progressing to death after three days. It was not possible to refer for resynchronization therapy or heart transplantation, due to psychiatric comorbidity, poor medication adherence and unavailability at the service. The precocious presentation of advanced and refractory HF, in this case, revels the importance of adherence to medication treatment, reduction of readmissions and the quick referral to a transplant center and ventricular support, in an attempt to reduce the morbidity and mortality of these patients.

**Keywords:** Chagas Cardiomyopathy; Chagas disease; Heart Failure.

**RESUMO:** A Doença de Chagas é responsável por 12 mil mortes anualmente nas Américas em decorrência da Cardiomiopatia Chagásica crônica (CCC) que ocorre em 20 a 30% dos infectados, após os 60 anos, 30 a 40 anos após a primo-infecção, levando à Insuficiência Cardíaca (IC) biventricular, arritmias, bloqueios e embolias. O diagnóstico é baseado na epidemiologia, quadro clínico, alterações eletrocardiográficas e de exames de imagem associados à sorologia. O presente estudo relata o caso de paciente com evolução atípica para a idade devido à rápida progressão para IC avançada e refratária, associada à alta morbimortalidade, manifestação tipicamente tardia da CCC. Caso clínico: paciente de 37 anos, sexo feminino, internada na Unidade de Terapia Intensiva de um hospital terciário no interior do Estado de São Paulo por IC congestiva descompensada, associada a derrame pleural. O ecocardiograma e sorologia para *Trypanossoma Cruzi* confirmaram o diagnóstico de CCC e risco de mortalidade estimado em 84%. Foi iniciado tratamento com betabloqueador, espironolactona, diurético, enalapril e paciente recebeu alta. Após 20 meses, reinternou com choque cardiogênico, síndrome cardiorrenal e fibrilação atrial tratados com diuréticos, inotrópicos e amiodarona, evoluindo para óbito após três dias. Não foi possível encaminhamento para terapia de ressincronização ou transplante cardíaco, devido à comorbidade psiquiátrica, má adesão medicamentosa e indisponibilidade no serviço. A precocidade da apresentação da IC avançada e refratária, neste caso, revela a importância da adesão ao tratamento medicamentoso, redução de reinternações e o rápido referenciamento a centro de transplante e suporte ventricular, como tentativa de diminuir a morbimortalidade desses pacientes.

**Palavras-chave:** Cardiomiopatia chagásica; Doença de Chagas; Insuficiência Cardíaca.

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## INTRODUCTION

Chagas disease is the third most prevalent parasitic disease, caused by *Trypanossoma Cruzi (T. Cruzi*), prevailing in Latin America[1-3]. The most recent estimates in Brazil regarding the number of people infected range from 1.9 to 4.6 million people, about 1.0 to 2.4% of the population[4].

Among patients infected with *T. Cruzi*, only 20% to 30% develop Chronic Chagasic Cardiomyopathy (CCC), which is the most serious condition of Chagas disease and usually occurs decades after the initial infection[5]. Chagas disease in its chronic form, in a habitual way, initially presents with no symptoms or alterations in the electrocardiogram or chest x-ray characterizing the Indeterminate Form, which can generally last from 30 to 40 years. After this period, patients can develop to the Determinate Form, without symptoms, with alterations in the exams, however, without ventricular dysfunction (B1) or with ventricular dysfunction (B2). Then, they develop to ventricular dysfunction and symptoms (C) and, finally, to the form with ventricular dysfunction and refractory symptoms (D)[6]. The typical evolution of this last phase is dilated cardiomyopathy, with bi-ventricular heart failure, and there may be a predominance of symptoms related to the involvement of the right ventricle, such as jugular stasis, hepatomegaly, ascites and lower limb edema. As symptoms, we can mention asthenia, dyspnea and atypical angina. The main complications involve ventricular arrhythmias, conduction disorders, abnormalities of the microcirculation, stroke and other systemic embolic events[7,8].

The report aims to describe the case of a young patient with Chagas Disease with severe and early cardiac manifestations and to analyze its evolution and complications, suggesting a form with faster evolution in young patients. This report was approved by the Research Ethics Committee (REC) of *Fundação Santa Casa de Misericórdia de Franca,* SP, Brazil with CAAE number 860662218.0.0000.5438 with previous collection of the Informed Consent Form (ICF). The information contained in the report was obtained through interviews with the patient and review of electronic medical records, and the reported tests were carried out in a tertiary hospital in Santa Casa de Franca and Hospital do Coração, a regional reference for patients with heart failure.

## CASE REPORT

CRC, female, 37 years old, resident and coming from São Paulo State and born in an endemic area of Chagas Disease in Brazil She was admitted to the Intensive Care Unit of *Hospital do Coração de Franca – SP* - Brazil, a tertiary hospital specialized in cardiological pathologies, being a reference in advanced heart failure in the region, in September 2017. She presented symptoms, which started four months before admission, of class III congestive heart failure according to the classification of New York Heart Association (NYHA)[9], without previous history of heart disease. At the time, IgG serology was requested for *T. Cruzi*, using the chemiluminescence and immunofluorescence method, which confirmed the diagnosis, with a value of 1/120. No serology was performed for IgM anti *T. Cruzi*, quantitative PCR and search for parasite in peripheral blood due to the unavailability of these tests at the service, and it is not possible to make a definitive diagnosis according to the criteria established by the World Health Organization and the current guidelines[10]. However, the patient had no fever in the last 60 days before admission and the clinical epidemiological criterion for the management of the case was considered as CCC in the Determined Form C. Despite the patient's origin, it was not possible to accurately identify the period in which the patient was contaminated because, on the date of the interview, the patient was unable to provide more specific information, however, we can infer that it occurred possibly between five and ten years before admission.

The echocardiogram made during hospitalization showed a left ventricular ejection fraction of 23%, with a diastolic diameter of the right ventricle of 67 mm, systolic pressure of pulmonary artery of 46 mmHg, enlargement of left and right cavities, with mild pericardial effusion, significant diffuse hypokinesia of left ventricle and right ventricle, mild to moderate mitral regurgitation and pulmonary arterial hypertension (Figures 1 and 2).

After starting treatment with beta-blockers, spironolactone, diuretic, enalapril, the patient showed clinical improvement and was discharged with the diagnosis of severe chagasic cardiomyopathy associated with decompensated heart failure profile B[11].

In February 2018, a 24-hour ambulatory electrocardiogram (Holter) was performed, which showed a predominant sinus rhythm, with a minimum heart rate (HR) of 28 bpm, an average HR of 52 bpm, a maximum HR of 128 bpm and, complete right branch block. In this Holter, 8,648 episodes of pauses lasting 2.0 seconds or more were recorded due to sinus bradycardia, sinus pauses, sinoatrial block and junctional bradycardia, with the longest pause being 5.1 seconds. 8,400 supraventricular extra-systoles were also observed, which are responsible for 13% of beats, an unsustained supraventricular paroxysmal tachycardia and three ventricular extra-systoles, showing an arrhythmogenic component in heart disease and the use of beta-blockers as the cause of pauses, however, without indication of pacemaker implantation or defibrillator.

In November of the same year, the patient was again hospitalized, in sickbay area of the same hospital, with syncope and dyspnea, and she was not using the prescribed drugs (carvedilol, spironolactone, enalapril

and furosemide). An electrocardiogram was performed, showing a first-degree atrioventricular block, right branch block and left atrial overload (Figure 3). Holter was repeated with improved pauses, with an average HR of 113 bpm. After stabilization, the patient was discharged from the hospital.

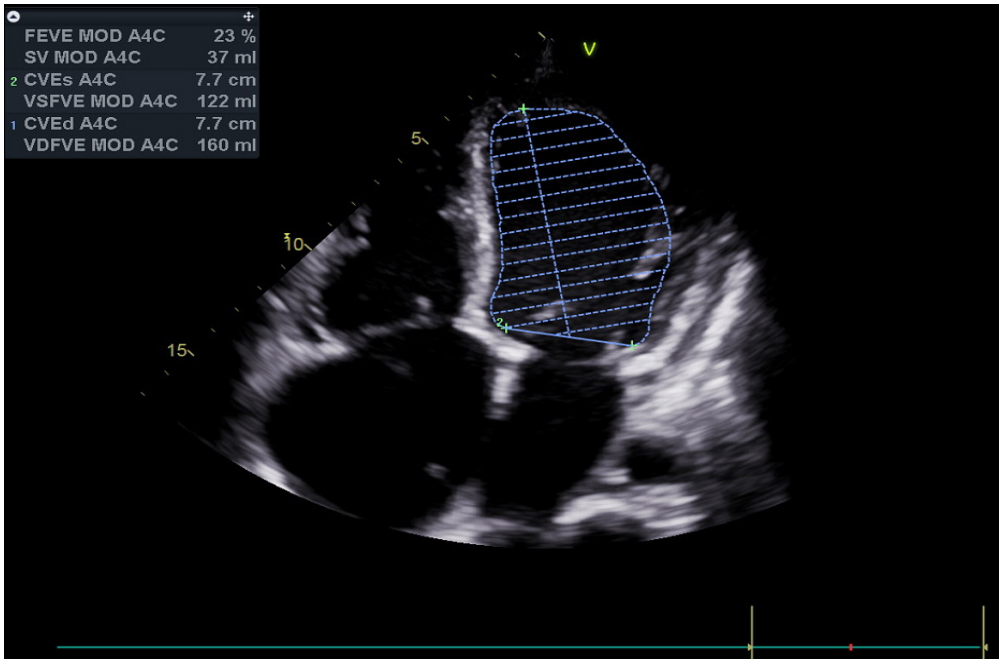



**Figure 1.** Echocardiogram: Ejection Fraction Measurement (Simpson method), Apical window Four Chamber. Ventricular ejection fraction: 23%

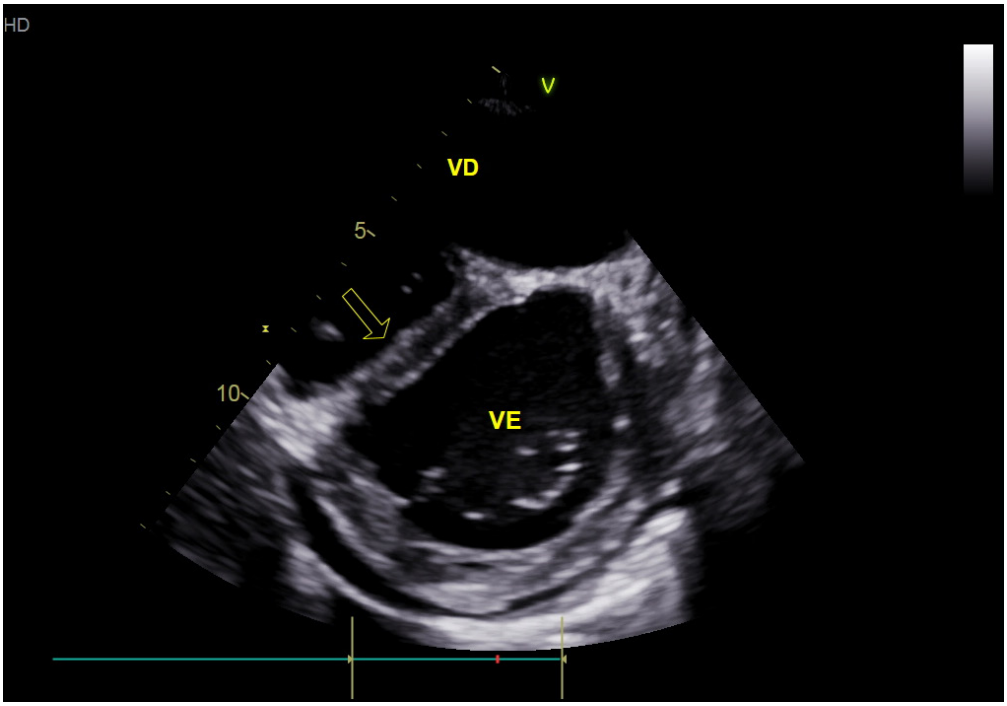
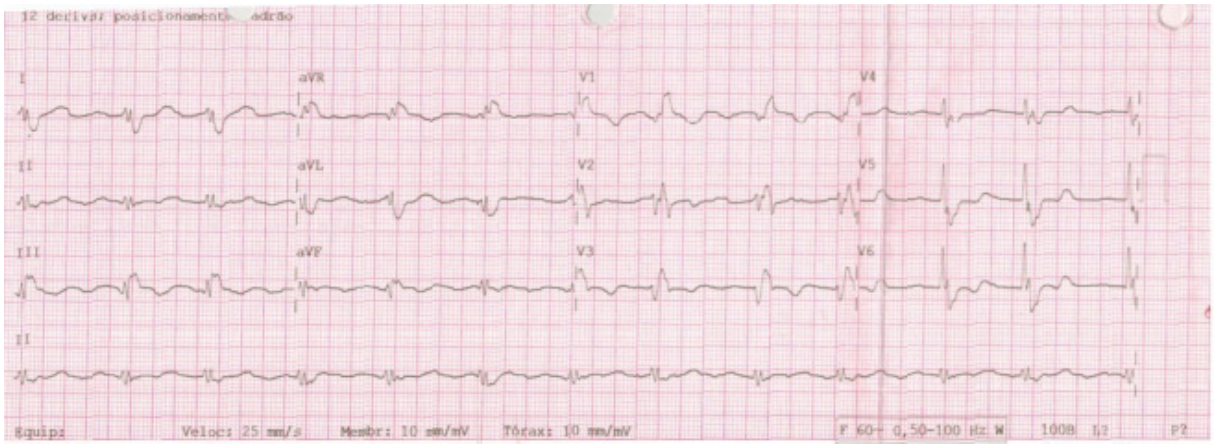


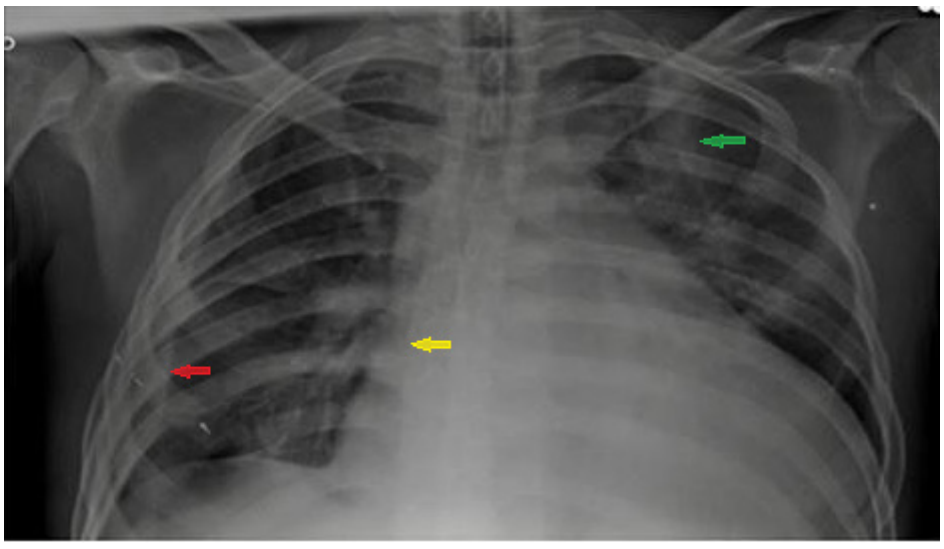

**Figura 2.** Deviation of Interventricular Septum into Left Ventricle due to pulmonary hypertension in diastole (D sign). Left parasternal window and short axis cut




Legend: HR – Heart Rate

**Figure 3.** Electrocardiogram. Sinus rhythm, HR 74 bpm, first-degree atrioventricular block, complete right branch block and left atrial overload

In April 2019, the patient was again admitted to the Intensive Care Unit with severe asthenia associated with arterial hypotension, drop in oxygen saturation and atrial fibrillation with HR of 170 bpm with indeterminate onset time. Electrical cardioversion was performed, followed by infusion of intravenous amiodarone and need for inotropic (Dobutamine), developing with stabilization of the hemodynamic state. During hospitalization, the patient presented a third heart sound, systolic murmur, of intensity 3 +/6+ in mitral focus, with inaudible blood pressure even with high doses of noradrenaline, jugular turgency and capillary filling time of 5 seconds. A chest x-ray was performed demonstrating an enlarged cardiac area, signs of pulmonary congestion, pleural effusion encysted on the right associated with alveolar veiling (Figure 4). She developed with changes in renal function and electrolytes, with progressive worsening of serum amount of urea, creatinine and, electrolytes, with hyperkalaemia, showing cardiorenal syndrome. After 72 hours, the patient died due to cardiogenic shock, with no possibility of renal replacement therapy, or other procedures, due to the severity of the evolution and hemodynamic instability.



Legend: CTI – Cardiothoracic Index

**Figure 4.** Chest x-ray. Enlarged cardiac area (CTI greater than 0.65 - cardiomegaly degree IV), signs of pulmonary congestion with cephalization of vascular network in the pulmonary apexes (green arrow), pleural effusion encysted on the right (red arrow), associated with alveolar veiling in the right base (yellow arrow)

The diagnostic hypotheses raised during the last hospitalization were: decompensated heart failure, profile C of chagasic etiology, associated with treatment abandonment, cardiorenal syndrome, persistent atrial fibrillation with undetermined time and cardiogenic shock.

## DISCUSSION

The natural history of Chagas disease comprises acute and chronic phases, with the chronic phase divided into indeterminate and determinate form. The indeterminate form, in general, is asymptomatic and lasts from 30 to 40 years[6], leading to symptoms in the sixth or seventh decade of life, when it becomes the determinate phase. However, according to Rassi, et al.[9], the asymptomatic phase can last from 10 to 30 years and only 30 to 50% of patients in this phase will develop CCC, being the most frequent and the most severe of complications and representing the determinate chronic form.

Regarding the diagnosis of Chagas disease by serological criteria, the time between the onset of symptoms and the collection of blood sample must be taken into account, in addition to clinical and epidemiological evidences. When detecting immunoglobulin M (IgM), the diagnosis of acute condition is made and the title ≥ 1:40 associated with IgG ≥ 1:80 should be considered as reagent. For confirmation by IgG marker, two collections are required with a minimum interval of 15 days between them, with the inclusion of the first and second samples in the same assay for comparative purposes[10]. In the diagnosis of chronic disease, it is necessary to combine two IgG tests that are reagent of different antigenic preparations or with different ways of achievements, which may be: ELISA (enzyme-linked immunosorbent assay), IFI (indirect immunofluorescence); HAI (indirect hemagglutination), WB (Western blot) or CLIA (chemiluminescence)[10].

The Latin American Guideline for the Diagnosis and Treatment of Chagas Heart Disease shows the CCC classification and through the interpretation of such stages, the patient in the report was admitted to the first hospitalization, already in stage C with bi ventricular dysfunction (see echocardiogram and case description)[6]. In her last hospitalization, there was a significant increase in creatinine and urea, characterizing a "cardiorenal syndrome", which can happen in up to 40% of patients with heart failure[11]. Due to the patient's hemodynamic instability and rapid evolution of the case, it was not possible to perform alternative methods such as ultrafiltration and dialysis, recommended by the current guidelines in these cases.

Patient's diagnostic research showed epidemiology and positive serology for *T. Cruzi*, suggestive electrocardiogram (see case description), echocardiogram with bi ventricular dysfunction, significant dilation of cardiac cavities and diffuse hypokinesia, which is more suggestive of Chagas heart disease than in others heart diseases[12]. In view of such cardiac manifestations and evolution, risk of death stratification for patients with CCC is an important tool/device in the prognosis, and can be assessed using Rassi Score (Table 1)[9].

**Table 1.** Rassi Score to risk of death stratification in a patient with Chagas heart disease

| Clinical feature | Score |
|---|---|
| Male gender | 2 |
| ECG with low voltage QRS | 2 |
| Non-sustained ventricular tachycardia | 3 |
| Global change or segmental mobility of VE | 3 |
| Chest x-ray cardiomegaly | 5 |
| Heart failure CF III/IV NYHA | 5 |

**Sourde:** Rassi et al.[9]

Based on this score, the patient had 13 points, representing a high risk of mortality (84 to 85%)[12]. The severity, recurrence and rapid progression of clinical manifestations presented by the patient would justify, in addition to the etiologic antiparasitic treatment, medication and non-medication for heart failure, the discussion of more specific and highly complex therapies, such as Cardiac Resynchronization Therapy (CRT) and heart transplantation.

With regard to etiological treatment of Chagas disease, the Clinical Protocol and Chagas Disease Therapeutic Guidelines[10] suggest two main antiparasitic drugs for reducing the parasitic load on the body, which are Benznidazole and Nifurtimox. The most used in Brazilian context is Benznidazole, which, despite the indication in the acute phase, is not recommended for chronic disease that is in the advanced phase[10]. In the BENEFIT study, it was observed that antiparasitic treatment with Benznidazole in patients with CCC did not prove to be effective in improving the course of the disease and that, despite the negative serology for *T. Cruzi*, it did not show a decrease in mortality and clinical outcomes[13].

In addition to antiparasitic medication treatment for Chagas disease, there are treatments for symptoms presented with the evolution of Chagas cardiomyopathy, which, in the case of this patient, predominated signs and symptoms of congestion and low cardiac output, requiring non medication treatment, based on water restriction, low sodium diet, vaccination against influenza and pneumococcus, physical exercise and drug treatment, mainly diuretics such as furosemide, angiotensin II-converting enzyme antagonists, inhibitors of aldosterone receptors and beta-blockers[14]. Despite all these conducts been prescribed for the patient, seeking treatment for stage C heart failure of functional class IV[11], following current guidelines, poor adherence to treatment made it impossible to assess therapeutic efficacy and reclassification to stage

D of Heart Failure.

Considering that CRT in CCC is a subject of intense discussion, it should be used predominantly in patients with optimized therapy and with left bundle branch block, characteristics not found in patient[14]. Heart transplantation represents the definitive therapy for treatment of HF, being also the treatment of choice for patients with end-stage Chagas disease cardiomyopathy[8]. However, the patient had exclusion criteria according to the 3rd Brazilian Cardiac Transplant Guideline[15], since she presented severe psychiatric comorbidity, low social support, low adherence to treatment and it was unavailable in the service in which she was hospitalized, which despite being a tertiary hospital, had no qualification for heart transplantation, resynchronization or defibrillator implantation by Unified Health System (Sistema Único de Saúde - SUS) and, the transference of the patient for other services was not possible due to the severity of the condition.

Due to the limitations of heart transplantation in CCC, such as the restricted access of patients to this therapy, prolonged waiting time for transplantation and the chance of reactivation of Chagas disease in the context of immunosuppression, new studies seeking new options for therapeutic strategies have been conducted. Among such innovative strategies is bone marrow cell transplantation. The report of the first human experience about bone marrow cell transplantation performed in patients with heart failure caused by Chagas disease was made by Vilas-Boas et al.[16] and shows to be effective and viable. This cell therapy was performed by intracoronary injection of mononuclear cells from autologous bone marrow, it was considered safe and a 20% relative increase in left ventricular ejection fraction (LVEF) can be obtained in patients who had significantly decreased in it[16]. Although the therapy is promising, it still needs more studies and investments, it not being accessible in most hospitals.

It is important to emphasize, in this case, the early onset of symptoms in the fourth decade of life, unusual age range for the presentation of the determinate chronic form of Chagas cardiomyopathy. In addition, the severity and accelerated progression of signs and symptoms, leading to early death, draw attention and encourage us to seek treatments that can slow down the progression of this form of disease.

## CONCLUSION

The presented report reveals disapproving clinical manifestations with rapid progression in young patient, such as heart failure, cardiogenic shock and cardiorenal syndrome, showing to have a worse prognosis and a high risk of mortality, according to Rassi Score. Early risk stratification is essential for a fast action in order to interrupt this accelerated evolution and control complications through appropriate therapeutic strategies, such as patient follow-up and monitoring, treatment of comorbidities and adherence to medication treatment, minimizing readmissions, in addition to directing ventricular support options and fast transference to a transplant center. There is also a need for further studies in young adult population in order to reduce morbidity and mortality in these cases, through therapies more accessible to the places where the disease is more prevalent.

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**Authors participation:** *Ana Flávia Parreira de Morais*: data collection from medical records, anamnesis with patient, development of summary, introduction, case report, discussion, and conclusion. *Dandara Freitas da Silveira e Souza*: data collection from medical records, anamnesis with patient, development of summary, case report, and discussion. *Murilo Henrique Fabri Tomazini*: development of summary, case report, discussion, and conclusion. *Rui Pereira Caparelli de Oliveira*: supervisor of the development of the case report, correction of technical aspects of the case report, collection of the patient's image exams and development of the case report, discussion, and conclusion. *Cynthia Kallás Bachur*: abstract translation and supervision on technical aspects of article writing.

## REFERENCES

1. Schmidt A, Filho AP, Neto JAM, Maciel BC. Epidemiologia no século XXI e aspectos clínicos da doença de chagas crônica. Rev Soc Cardiol Estado de São Paulo. 2016;26(4):230-3. Disponível em: http://socesp.org.br/revista/edicoes-anteriores/volume-26-n4-outubro-dezembro-2016/epidemiologia-no-seculo-xxi-e-aspectos-clinicos-da-doenca-de-chagas-cronica-/549/79/.
2. Bocchi EA, Mendea TM, Issa VC. Novas abordagens terapêuticas na doença de chagas: terapia celular, anticorpos, aférese. Rev Soc Cardiol Estado de São Paulo. 2016;26(4):261-5.
3. Silva HC, Aras R, Galdame AMA, Martinez-Silveira MS, Grassi MFR, Silva RJ et al. Avaliação clínica na atenção primária e infectologia dos pacientes com doença de Chagas na forma crônica. Rev Baiana Saúde Pública. 2013;37(supl. 1):7-21.
4. Dias JC, Ramos Jr. NA, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, et al. II Consenso Brasileiro em Doença de Chagas, 2015. Epidemiol Serv Saúde (Brasília). 2016;25:7-86. doi: 10.5123/s1679-49742016000500002.
5. Junior ASM, Lopes CC, Cavalcante PF, Martins E. Chronic Chagas cardiomyopathy patients and resynchronization therapy: a survival analysis. Braz J Cardiovasc Surg. 2018;33 (1):82-8. doi: https://doi.org/10.21470/1678-9741-2017-0134.
6. Andrade JA, Marin-Neto JA, Paola AAV, Vilas-Boas F, Oliveira GMM, Bacal F, et al. Sociedade Brasileira de

Cardiologia. I Diretriz Latino Americana para o Diagnóstico e Tratamento da Cardiopatia Chagásica. Arq Bras Cardiol. 2011;97(2 supl.3):1-48.

7. Nunes MC, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverria LE, Dutra WO, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. Circulation. 2018;138:169-209. doi: https://doi.org/10.1161/CIR.0000000000000599.

8. World Health Organization. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec hebdomadaire, 2015;90(6):33-44. https://apps.who.int/iris/handle/10665/242316.

9. Rassi Jr A, Rassi A, Marin-Neto JA. Chagas heart disease: pathophysiologic mechanisms, prognostic factors and risk stratification. Mem Inst Oswaldo Cruz. 2009;104(Suppl 1):152-8. doi: https://doi.org/10.1590/S0074-02762009000900021

10. Brasil. Ministério da Saúde. Comissão Nacional de Incorporação de Tecnologias no SUS. Protocolo clínico e diretrizes terapêuticas doença de Chagas, n.397. Brasília, DF; 2018.

11. Sociedade Brasileira de Cardiologia. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: https://doi.org/10.5935/abc.20180190.

12. Simões MV, Romano MMD, Schmidt A, Martins KSM, Marin-Neto JA. Cardiomiopatia da Doença de Chagas. Int J Cardiovasc Sci. 2018;31(2):173-89. doi: https://doi.org/10.5935/2359-4802.20180011.

13. Morillo CA, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi A, Jr., Rosas F, Vellena E, Quiroz R, Bonilla R, Britto C, Guhl J, Mattos A, Lazdins J, Rassi A, Connoly SJ, Yusuf S, BENEFIT Investigators. Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy. N Engl J Med. 2015;373:1295-306. doi: https://doi.org/10.1056/NEJMoa1507574

14. Bestetti RB. Cardiomiopatia chagásica crônica: diagnóstico e tratamento. Rev Soc Cardiol Est São Paulo. 2016;26(4):246-52.

15. Bacal F, Marcondes-Braga FG, Rohde LEP, Júnior JLX, Brito FS, Moura LZ, et al. 3ª Diretriz Brasileira de Transplante Cardíaco. Arq Bras Cardiol. 2018;111 (2):230-89. doi: https://doi.org/10.5935/abc. 20180153.

16. Vilas-Boas F, Feitosa G, Soares M, Pinho-Filho J, Mota A, Almeida A, et al. Transplante de células da medula óssea na insuficiência cardíaca chagásica: relato da primeira experiência humana. Arq Bras Cardiol São Paulo. 2011;.96. doi: https://doi.org/10.1590/S0066-782X2011005000028.

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