

Successful treatment of suspected early form of chronic Chagas cardiomyopathy: a case report

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Background

Chagas disease, caused by the protozoan *Trypanosoma cruzi*, is the most common parasitic aetiology of non-ischaemic cardiomyopathy in the Americas, causing significant morbidity and mortality. The clinical spectrum ranges from early asymptomatic disease to severe cardiac manifestations including dilated cardiomyopathy, heart failure, dysrhythmias, conduction abnormalities, thromboembolism, and sudden death.

Case summary

We present a case of Chagas disease in a 75-year-old patient originally from El Salvador who presented to our Canadian tertiary centre with heart failure and atrial fibrillation/flutter. The patient had dilated cardiomyopathy with severely reduced systolic function, which was thought to be early Chagas cardiomyopathy after confirmatory positive serologies for *T. cruzi*. The patient demonstrated significant clinical improvement and recovery of systolic function with benznidazole therapy that was sustained up to 12 months on follow up.

Discussion

The American Heart Association recommends considering treatment of early chronic Chagas cardiomyopathy with anti-trypanosomal therapy. Our case highlights the importance of multidisciplinary collaboration in the diagnosis of early Chagas cardiomyopathy and critical timing of benznidazole, as effectiveness is limited in late disease due to myocardial cell-death programme. Although the historical BENEFIT study is known to not have shown mortality reduction, we advocate that the significant reduction in cardiovascular-related hospitalizations should be considered for symptomatic patients with early Chagas cardiomyopathy with the potential benefit of improving cardiac function and avoiding need for heart transplantation.

Keywords

Chagas disease • Cardiomyopathy • Trypanosoma • Benznidazole • Tropical medicine • Case report

ESC Curriculum

6.5 Cardiomyopathy • 6.1 Symptoms and signs of heart failure • 5.4 Atrial flutter • 5.6 Ventricular arrhythmia • 5.3 Atrial fibrillation

Primary specialties involved other than cardiology

Infectious diseases, clinical microbiology, pharmacy.

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Learning points

- Chagas disease is the most common parasitic cause of non-ischaemic cardiomyopathy in the Americas, yet diagnosis and management can be challenging.
- A multidisciplinary approach involving cardiologists, infectious disease specialists, and clinical microbiologists is recommended for diagnosis of early Chagas cardiomyopathy and potential treatment with benznidazole.
- Benznidazole should be considered for symptomatic patients with suspected early Chagas cardiomyopathy, as this presents the opportune timing to derive benefit and may prevent further cardiovascular-related hospitalization as well as avoid end-stage cardiomyopathy that would require heart transplantation.

Introduction

Chagas disease, also known as American trypanosomiasis, is caused by the protozoan parasite *Trypanosoma cruzi*. The Brazilian clinician-scientist, Dr Carlos Chagas, first discovered this parasite being transmitted to humans from the faeces of the vector Triatominae, a blood-sucking insect in the subfamily of Reduviidae.¹ This contrasts with other *Trypanosoma* diseases such as Human African Trypanosomiasis, which is transmitted through the saliva of the tsetse fly (Figure 1). Originally endemic to Latin America with the highest prevalence in Bolivia, Argentina, and Paraguay, an estimated 6 million people are now infected with Chagas disease globally through import by infected hosts from Latin America who have been in contact with the infected reduviid insect in an endemic region.¹ The clinical presentation of Chagas disease is classified as acute, chronic, indeterminant, or congenital. Periorbital swelling, also known as Romaña sign or Chagoma, is indicative of the portal of entry for the parasite. Since 2006, many western countries have implemented screening for American trypanosomiasis to prevent transmission by transfusion or solid organ transplant. The chronic form can manifest several years after initial infection and involves target organs including cardiac, digestive, autonomic, sensory, motor, and central nervous system.¹ The congenital form is recognized more as an important part of vertical transmission.

Timeline

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|--------|---|
| Week 1 | <ul style="list-style-type: none"> • Initial presentation to hospital with shortness of breath • Investigations consistent with heart failure and atrial fibrillation/flutter; left-ventricular ejection fraction (LVEF) 15–20% • Electrical cardioversion to sinus rhythm; LVEF 30–35% • Negative myocardial perfusion imaging • Discharge with pending non-ischaemic cardiomyopathy workup |
| Week 2 | <ul style="list-style-type: none"> • Positive serology for <i>T. cruzi</i> |
| Week 3 | <ul style="list-style-type: none"> • Presents again with heart failure and atrial flutter • Self-converts to sinus rhythm and discharge • Syncopal event at home and returns next day in ventricular tachycardia (VT) • Shocks to sinus rhythm and CRT-D implantation; LVEF 25–30% • Multidisciplinary discussion involving cardiology, infectious diseases, and clinical microbiology. Early Chagas cardiomyopathy suspected and benznidazole requested via Health Canada Special Access Programme • Discharge with close follow up while awaiting benznidazole import |

Continued

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|---------|---|
| Week 7 | <ul style="list-style-type: none"> • Clinical follow up with ongoing New York Heart Association (NYHA) Class II symptoms; unchanged LVEF 25–30% |
| Week 11 | <ul style="list-style-type: none"> • Benznidazole arrives and initiated at 150 mg PO BID ×60 days |
| Week 16 | <ul style="list-style-type: none"> • Significant clinical improvement to NYHA Class I |
| Week 20 | <ul style="list-style-type: none"> • Completed full 60-day course of benznidazole therapy |
| Week 24 | <ul style="list-style-type: none"> • Improved LVEF 45–50% |
| Week 72 | <ul style="list-style-type: none"> • Stable LVEF 60% a year after finishing benznidazole therapy • NYHA Class I and full return to activities of daily living |

Approximately, 20–40% of patients infected with *T. cruzi* develop Chagas cardiomyopathy, making it the most common parasitic cause of non-ischaemic cardiomyopathy in the Americas.² Microvascular derangements driven by parasite-induced immune responses result in various cardiac manifestations including dilated cardiomyopathy, heart failure, dysrhythmias, conduction abnormalities, thromboembolism, and sudden death.¹ As the disease progresses to end-stage cardiomyopathy, apoptosis or myocardial cell-death programme occurs with few surviving intracellular parasites and, as a result, the heart is no longer responsive to anti-trypanosomal treatment with benznidazole. We present a patient case with confirmed Chagas disease progressing towards probable early cardiomyopathy/carditis with several aforementioned cardiac complications who demonstrated significant and sustained clinical response to treatment with benznidazole due to timely and appropriate patient selection.

Case presentation

A 75-year-old expatriate female who had recently returned from her home country of El Salvador presented to our Canadian Tertiary Centre with progressive shortness of breath, orthopnoea, and syncopal episodes over the preceding month. She had no chest pain, gastrointestinal, or neurological symptoms. She first emigrated from El Salvador to Canada 30 years ago. Her medical history was significant for hypertension, Type 2 diabetes, and chronic kidney disease (baseline eGFR 30 mL/min/1.73 m²). Her home medications included nifedipine 60 mg once daily, metformin 1 g twice daily, glimepiride 30 mg once daily, and linagliptin 2.5 mg twice daily. She was afebrile (36.2°C) with a blood pressure of 103/73 mmHg, a heart rate of 138 beats per min (b.p.m.), and oxygen saturation of 97% on room air. Electrocardiogram (ECG) demonstrated new onset atrial flutter/fibrillation, with left anterior fascicular block, prolonged QTc of 512 ms. Additional investigations supported congestive heart failure with NT pro-BNP measuring 15 600 ng/L (normal range ≤125 ng/L), high-sensitivity troponin T 21 ng/L (normal range <14 ng/L), and an enlarged cardiac silhouette on chest X-ray. Transthoracic echocardiogram (TTE) revealed an

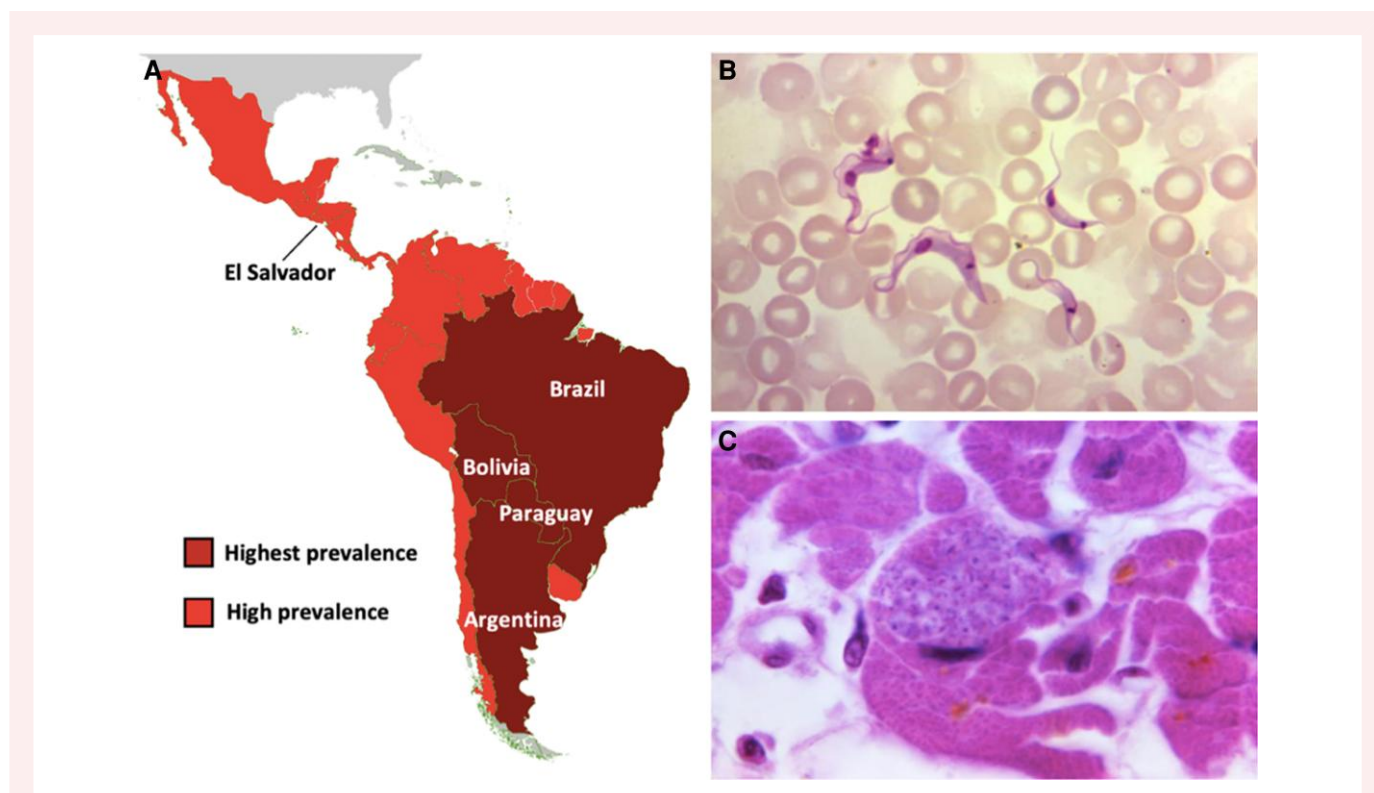


Figure 1 (A) Chagas disease prevalence in Latin America. (B) *Trypanosoma cruzi* parasites in a blood sample specimen. (C) *Trypanosoma cruzi* amastigotes in myocardial tissue causing apoptosis. All images courtesy of the Centers for Disease Control and Prevention under the Public Health Image Library, which is free of copyright restrictions.

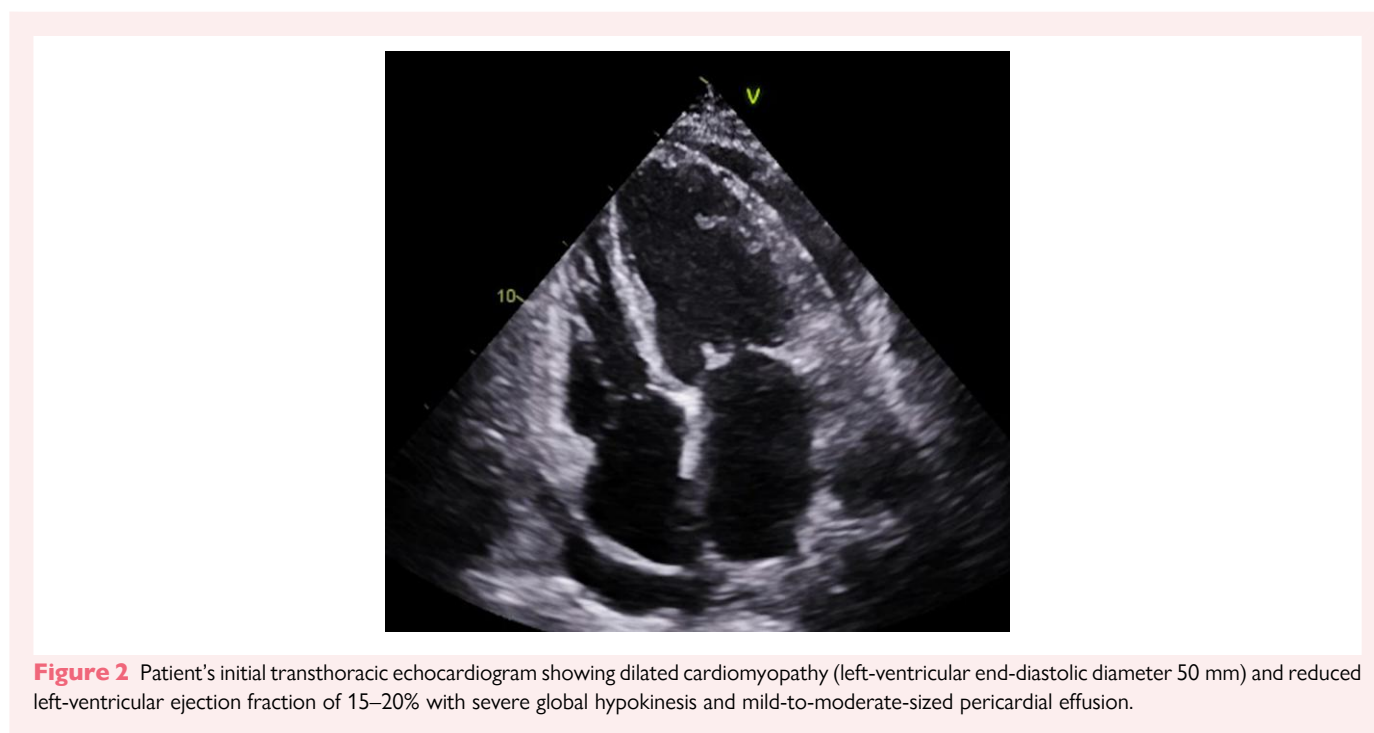


Figure 2 Patient's initial transthoracic echocardiogram showing dilated cardiomyopathy (left-ventricular end-diastolic diameter 50 mm) and reduced left-ventricular ejection fraction of 15–20% with severe global hypokinesia and mild-to-moderate-sized pericardial effusion.

LVEF of 15–20% with severe global hypokinesia, left-ventricular end-diastolic diameter (LVEDD) of 50 mm, mild tricuspid and mitral regurgitation, and a mild-to-moderate-sized pericardial effusion (Figure 2). Transoesophageal echocardiogram confirmed no thrombus, and the patient underwent direct-current cardioversion. Restoration of sinus rhythm provided substantial symptom improvement and return of her ejection fraction to previous baseline of 35%. Unfortunately, she later developed cardiogenic shock due to ongoing volume overload and required IV furosemide 40 mg twice daily with IV infusion of milrinone upwards of 0.375 µg/kg/min for 3 days. Myocardial perfusion imaging showed no reversible ischaemia and sustained LVEF of 30–35%. She was stabilized off inotropic support and discharged on metoprolol 25 mg twice daily, amiodarone 200 mg once daily, nitroglycerin 0.2 mg/h patch, hydralazine 100 mg three times a day, furosemide 20 mg once daily, and apixaban 2.5 mg twice daily for a CHADS₂ score of 4. Further left-ventricular (LV) enhancement therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) was not initiated due to acute on chronic kidney impairment. Workup for non-ischaemic cardiomyopathy revealed a normal thyroid-stimulating hormone, normal ferritin, and unremarkable serum and urine protein

electrophoresis. However, serology was positive for *T. cruzi* IgG antibody by ELISA IgG and confirmed by an immunoblot assay. Both tests were done at the National Reference Centre for Parasitology in Montreal, Canada, and reviewed by clinical microbiologists.

She represented to hospital 3 weeks later with a new congestive heart failure symptomatology and suspected pneumonia. Initial ECG revealed atrial flutter. However, she self-converted to sinus rhythm and clinically improved with diuresis and antibiotics. She was discharged but returned to the emergency department the same day after witnessed syncope at home. She was bradycardic on arrival (heart rate 37 b.p.m.) and then developed conscious polymorphic VT (Figure 3). Her potassium was low at 2.4 mmol/L (normal range 3.5–5.0 mmol/L) with a magnesium of 0.8 mmol/L (normal range 0.7–1.2 mmol/L) and a prolonged QTc of 663 ms. She required 3 shocks for recurrent VT and was stabilized with a temporary pacemaker, potassium, and magnesium supplementation. She did not require cardiopulmonary resuscitation. TTE revealed LVEF 25–30% with a moderate-sized circumferential pericardial effusion without tamponade that was not amenable to pericardiocentesis. She received cardiac resynchronization therapy with defibrillator (CRT-D) implantation prior to discharge due to multiple indications including

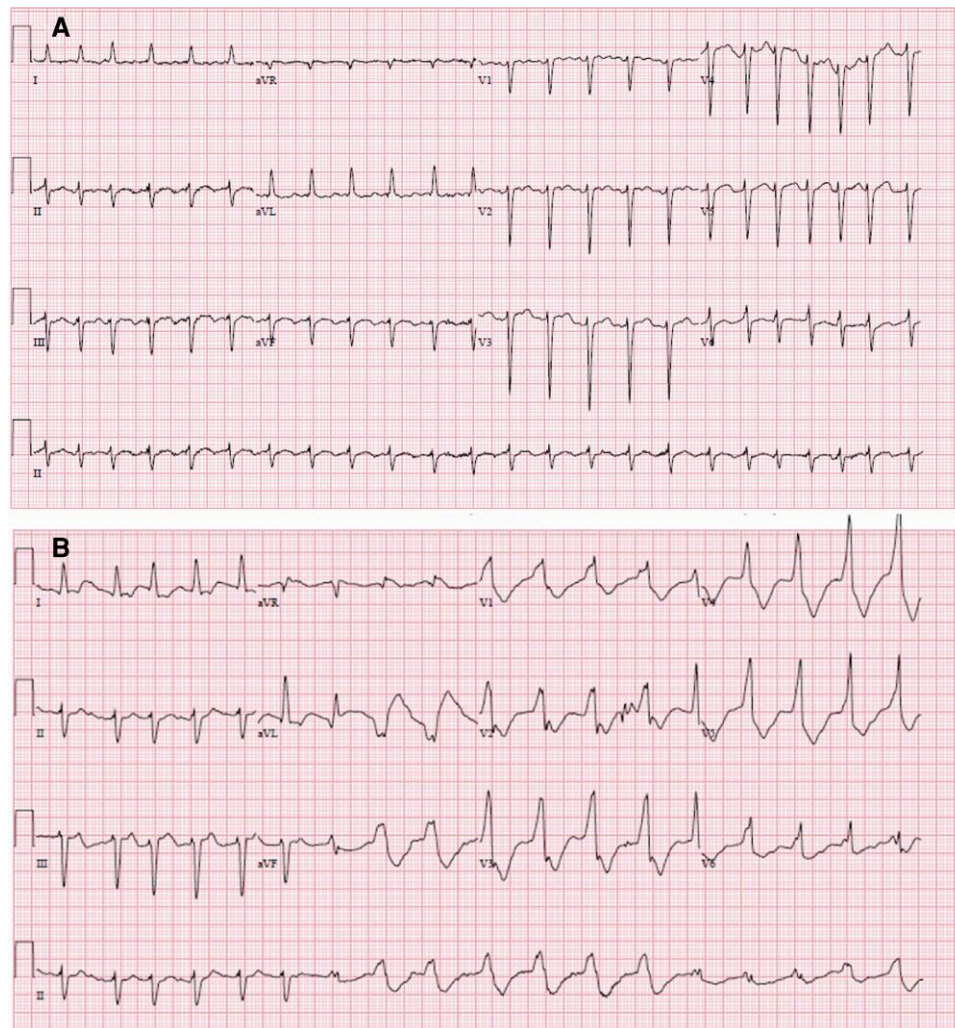


Figure 3 Patient electrocardiograms. (A) Atrial flutter with variable conduction and left anterior fascicular block with QTc 512 ms. (B) Progression from atrial flutter with variable conduction and left anterior fascicular block to wide complex tachycardia resembling polymorphic ventricular tachycardia with prolonged QTc 663 ms.

recurrent VT, reduced LVEF, and widened QRS concerning for need for biventricular pacing. She was not a favourable candidate for cardiac ablation due to her age. At this time, she was initially thought to have end-stage cardiomyopathy given her symptoms and reduced LVEF. However, on multidisciplinary discussion between the infectious diseases and cardiology teams, it was concluded that the acute reduction in LVEF was due to atrial flutter/fibrillation and once the dysrhythmia was abolished, the improved LVEF and global hypokinesia with upper limit of normal LVEDD would be more in keeping with early Chagas cardiomyopathy. The constellation of clinical findings, the patient demographic origin, and positive serology with confirmatory immunoblot assay strongly pointed to this sequelae being most probably due to Chagas disease. While a cardiac MRI would have been valuable, it was not feasible given her renal function and the prolonged wait time for this modality during the current COVID-19 pandemic. Therefore, the plan was to initiate treatment with benznidazole, the primary anti-trypanosomal agent approved by Health Canada. Benznidazole was requested from South America via the Health Canada Special Access Programme and arrived at our hospital ~8 weeks later.

The patient remained stable with NYHA Class II symptoms when seen a month later in outpatient follow up. Device interrogation showed 97% biventricular pacing with underlying sinus bradycardia. Repeat TTE revealed stable LVEF 25–30% and moderate-to-severe global hypokinesia. She received benznidazole 150 mg orally twice daily for 60 days (equivalent to 5 mg/kg/day for a 60-day course). The patient tolerated this medication well with no adverse effects, which commonly include abdominal pain, dermatitis, leukopenia, weight loss, or peripheral neuropathy.² One month after completing benznidazole therapy, she reported significant symptom improvement with baseline NYHA Class I symptoms and no further syncope episodes or CRT-D shocks. She did not develop other complications of Chagas disease such as gastrointestinal symptoms, thromboembolism, or syncope episodes. She remained on metoprolol 150 mg twice daily, hydralazine 100 mg three times a day, furosemide 20 mg once daily, and apixaban 2.5 mg twice daily. Repeat TTE several weeks after completing benznidazole showed improved LVEF of 45–50% with regression towards mild hypokinesia. She has ongoing follow up with cardiology and infectious diseases services, demonstrating sustained cardiac functional improvement even 12 months later with an LVEF of 60% and reversal of hypokinesia to normal global function.

Discussion

Chagas cardiomyopathy is associated with poor prognosis even when compared with other forms of cardiomyopathy including hypertensive and ischaemic causes.⁴ Risk stratification scores such as the Rassi score have been validated to predict mortality in chronic Chagas cardiomyopathy, which marks an intermediate risk or ~18% 5-year mortality rate when applied to our patient.⁵ Therefore, it is imperative and essential that early cardiomyopathy is differentiated from late cardiomyopathy (Figure 4), as the former may be potentially responsive to treatment while the latter has reached a state of myocardial cell-death programme where medical therapy has poor or no response.

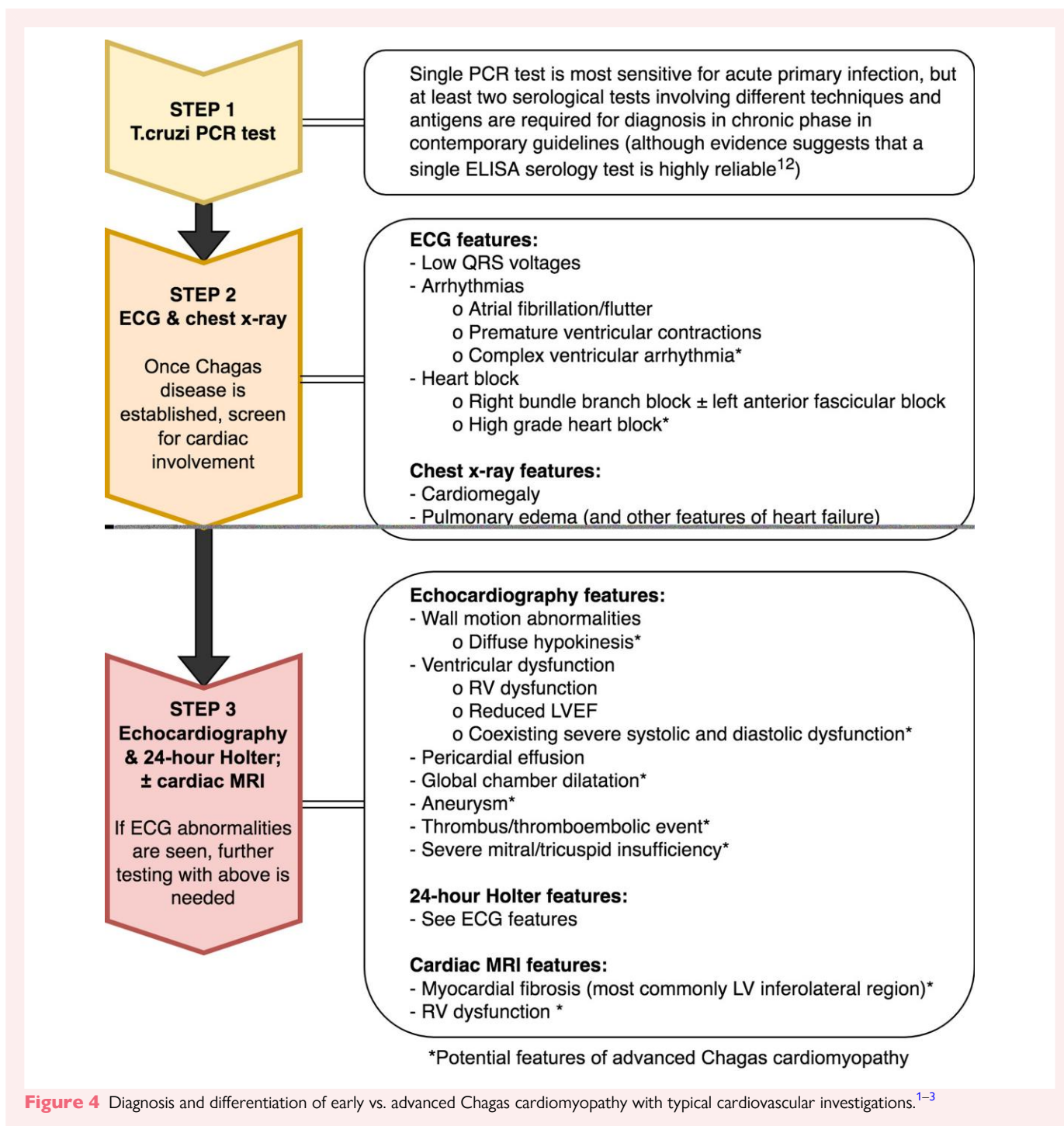
Chronic Chagas cardiomyopathy can be staged based on severity (Table 1). Indeterminate form has no subjective or objective evidence of any organ involvement. However, a good portion during indeterminate stage is shown to have subclinical early cardiomyopathy/carditis. The transition from intermediate to early form of chronic cardiomyopathy is typically marked by conduction abnormalities on ECG, which include atrial arrhythmia and right bundle branch block, with or without left anterior fascicular block.^{1,3} Mild right-ventricular dysfunction, reduced LVEF, wall motion abnormalities, and features of myocarditis can also be seen on echocardiography in early form of disease.³ In contrast, advanced or late forms manifests as significant dilated cardiomyopathy, marked by global chamber dilatation with diffuse hypokinesia and severe mitral

and tricuspid insufficiency.^{2,3} In addition to severe coexisting systolic and diastolic dysfunction, other structural abnormalities such as aneurysms, thrombus, or features of chronic myocarditis can be seen.¹ Accompanying electrical anomalies include complex ventricular tachyarrhythmia or high-grade heart blocks in advanced disease.³ The substrates for ventricular arrhythmias derive from fibrotic myocardial lesions, with the most common focus being the LV inferolateral region.¹ The extent of myocardial fibrosis seen by late gadolinium enhancement on cardiac MRI correlates with disease severity and has been associated with increased risk of cardiovascular death and sustained VT.^{1,2} Altogether, these features of established advanced cardiomyopathy signify an increased risk for sudden cardiac death.¹

Contemporary evidence for anti-trypanosomal therapy in chronic Chagas cardiomyopathy is limited and primarily supports treating the indeterminate stage or early forms of cardiomyopathy but not the established advanced disease (Table 1). The BENEFIT study is the largest randomized control trial to date that included 2854 patients with established Chagas cardiomyopathy from South America with mean LVEF 55% and NYHA Classes I–II symptoms.⁶ These patients were followed over 5 years after completing 40–80 days of benznidazole 300 mg daily. There was not a significant reduction in all-cause or cardiovascular mortality (27.5 vs. 29.1%, $P = 0.31$; 13.6 vs. 14.3%, $P = 0.55$), although there was a significant reduction in hospitalization from cardiovascular causes (16.9 vs. 20.1%, $P = 0.03$). In contrast, studies in early chronic Chagas cardiomyopathy have suggested clinical benefit, though they were all non-randomized studies. The SaMi-Trop observational study of 1813 patients demonstrated reduced all-cause mortality at 2 years with a 60-day course of benznidazole (odds ratio 0.37, 95% confidence interval 0.21–0.63).⁷ One modest study of 566 patients showed less frequent clinical progression after a median 9.8-year follow up from a 30-day course of benznidazole,⁸ while another smaller study of 310 patients revealed lower rates of ECG changes after a 20-year follow up from a 60-day course.⁹ More recently, a retrospective cohort study of 228 patients from Brazil demonstrated lower cumulative progression incidence of chronic indeterminate to cardiomyopathy form (7.9 vs. 21.1%, $P = 0.04$) after a median 15.1-year follow up from 30 to 60 days of benznidazole.¹⁰

Based on the available evidence, the 2018 American Heart Association scientific statement on Chagas cardiomyopathy recommends anti-trypanosomal treatment to only be offered to patients with early stages of chronic Chagas cardiomyopathy; treatment should not be given in established dilated cardiomyopathy.¹ However, interpretation of the latter statement is left to the clinician as established dilated cardiomyopathy could refer to severity or chronicity vs. presence of disease in general, which may be amendable to therapy in early stages. Anti-trypanosomal agents are likely ineffective in late chronic disease due to apoptosis and fibrosis of myocardial cells involved in the pathogenesis of irreversible heart failure (Figure 1).¹¹ In these advanced stages, alternative treatment through symptom management or heart transplantation should be considered.

For scientific discussion, our patient meets the contemporary gold standard for diagnosis of Chagas disease with a positive serology and confirmatory immunoblot assay. However, a clinical diagnosis could likely have been made based on the initial positive serological test alone supported by the constellation of patient demographic origin and clinical findings. Literature review of Chagas diagnostic testing reveals that ELISA serology tests are highly reliable even as a standalone test with high sensitivity and specificity, while polymerase chain reaction molecular tests have poor sensitivity and their reliability have never been studied in the context of Chagas disease.¹² Most importantly, further delay in patient diagnosis, which can be disrupted during these contemporary times by the COVID-19 pandemic, may impede the opportune time to start effective treatment during the early stages of cardiomyopathy. On that note, our patient could have been misclassified as severe chronic Chagas cardiomyopathy based on her significant heart failure symptoms that led to cardiogenic shock and ventricular arrhythmias that required CRT-D implantation. However,



her transient improvement in LVEF with restoration of sinus rhythm from atrial flutter/fibrillation early on in hospitalization suggested that her disease was likely more consistent with early form of cardiomyopathy as opposed to established advanced cardiomyopathy. Her LVEDD at the upper limit of normal per reference values of the 2015 American Society of Echocardiography guidelines also suggested that her LV dilatation was not severe or chronically established.¹³ Therefore, she should have potentially benefitted from anti-trypanosomal therapy based on the supporting evidence discussed above, which was confirmed objectively with improved LVEF on echocardiography and subjectively by the patient with symptom relief following benznidazole treatment without further LV enhancement

therapy with ACEI or ARB. While the BENEFIT study was negative for the mortality endpoint, the significant reduction in hospitalization from cardiovascular causes should not be taken lightly in treating symptomatic patients such as ours with probable early Chagas cardiomyopathy. Her cardiac function improved within a few weeks after completion of benznidazole therapy and she did not have further readmissions to hospital compared with her initial frequent readmissions while she was only treated with typical cardiac medications and device therapy. Her marked improvement with benznidazole also argues against the alternative diagnosis of tachycardia-induced cardiomyopathy from her intermittent atrial flutter.

Table 1 Chronic Chagas cardiomyopathy staging and treatment recommendation

Indeterminate form	Chagas cardiomyopathy				
	A	B		C	D
	Evidence of structural disease but no signs or symptoms of heart failure				
	B1	B2			
Asymptomatic and unremarkable physical examination. Normal ECG, chest X-ray, and no evidence structural cardiomyopathy	Normal global ventricular function with preserved LVEF	Global ventricular dysfunction with reduced LVEF	LV dysfunction with current or previous symptoms of heart failure (NYHA Classes I–IV)	Refractory heart failure despite optimized medical therapy	
Treat with anti-trypanosomal therapy	Treat with anti-trypanosomal therapy	Treat with anti-trypanosomal therapy	Treat with anti-trypanosomal therapy or consider alternative therapy	Consider alternative therapy	
<p>Spectrum of advanced cardiomyopathy: Global chamber dilatation with diffuse hypokinesia, severe mitral/tricuspid insufficiency, coexisting severe systolic and diastolic dysfunction, complex ventricular arrhythmia, high-grade heart block, aneurysms, thromboembolic event, chronic myocarditis, sudden cardiac death</p> <p>Consider alternative treatment</p>					

Adapted from Andrade JP et al. *Arq Bras Cardiol* 2011 and AHA Update on Chagas Cardiomyopathy. *Circulation* 2018.^{1,3}
LVEF, left-ventricular ejection fraction; LV, left ventricular; NYHA, New York Heart Association.

Conclusion

In summary, our case emphasizes the importance of timely diagnosis and shared decision making in treating suspected early forms of Chagas cardiomyopathy. The best time to treat Chagas is during the indeterminate stage before any target organ involvement, which yields the most favourable results. However, when cardiac involvement is identified, it is critical to further stratify patients into early vs. advanced cardiomyopathy as the former will potentially still benefit from benznidazole therapy. Multidisciplinary collaboration between cardiologists, infectious disease, and clinical microbiologists is imperative for optimal selection of candidates for treatment and ongoing clinical follow up of early Chagas cardiomyopathy. Larger studies and randomized control trials are needed to further elucidate long-term effect on morbidity and mortality when treatment is initiated during early phases of Chagas cardiomyopathy.

Lead author biography



Dr Nelson Lu is an Internal Medicine resident at the University of British Columbia in Canada. His primary academic interest is in cardiology and his research work broadly includes management of arrhythmia and cardiomyopathy.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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