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Trypanosoma cruzi infection: a review with emphasis on cutaneous manifestations

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Abstract

Chagas disease, an infection caused by the protozoan *Trypanosoma cruzi* and transmitted by the Reduuvid insect vector, remains a major cause of morbidity in Central and South America over a century after its discovery in 1909. Though major advances in preventing the spread of this disease have been made in recent decades, millions of individuals remain chronically infected due to prior exposure to *T. cruzi* and are at risk for future complications from the disease. Dermatologic manifestations of acute infection may include localized swelling at the site of inoculation (chagoma), conjunctivitis (Romaña's sign), and a generalized morbilliform eruption (schizotrypanides). Reactivation of quiescent infection in immunocompromised hosts due to the acquired immunodeficiency syndrome or organ transplantation can present with fever and skin lesions including panniculitis. The wide-spread emigration of chronic carriers of *T. cruzi* to North America, Europe, and Australia makes it imperative that dermatologists worldwide be familiar with this entity to ensure proper diagnosis and treatment.

Introduction

Chagas disease is an infection caused by the protozoan parasite *Trypanosoma cruzi*.[1] Endemic to large portions of Latin America, with the exception of the Caribbean, this disease in recent decades has increasingly been diagnosed worldwide because of global travel and large-scale emigration from Latin America to North America, Europe, and Australia.[2] In addition, Chagas disease is now appreciated to be an opportunistic infection in immunocompromised individuals, including those with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).[3] Both acute natural infection and recrudescence of infection observed in immunocompromised individuals may present with cutaneous lesions. This article reviews the pathogenesis, diagnosis, and treatment of Chagas disease, with an emphasis on its cutaneous manifestations.

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Conflicts of interest: None to report.

Life cycle

The parasite has a complex life cycle (Fig. 1). Over 100 species of Triatominae (Hemiptera: Reduviidae) can serve as insect vectors for *T. cruzi*. These vectors are found throughout Latin America and even in the southern USA, especially in rural areas.[4] During a blood meal from an infected mammalian host, the insect vector ingests blood form trypomastigotes, which undergo transformation to epimastigotes. Within 3–4 weeks, infective, non-dividing metacyclic trypomastigotes present in the hindgut of the vector are deposited with the feces of the vector during subsequent blood meals.[5] Transmission to the new host occurs when the parasite-laden feces contaminate oral or nasal mucous membranes, the conjunctiva, and other surfaces.[6] The trypomastigotes enter a host cell and transform into intracellular amastigotes, which then multiply by binary fission and ultimately transform into blood form trypomastigotes, which are released as the host cell ruptures. These trypomastigotes infect adjacent cells or disseminate via the lymphatics and the bloodstream and infect new cells.[5] Although any nucleated mammalian cell can be parasitized, the cells of the cardiovascular, reticuloendothelial, nervous, and muscular systems as well as adipose tissue are favored.[7] Another mode of transmission is via blood transfusion. Although transfusion-associated Chagas disease was always less common than insect-transmitted Chagas disease, the frequently severe nature of transfusion-associated Chagas disease necessitated the implementation of blood donor screening programs. Subsequently, the incidence of transfusion-associated Chagas disease in endemic countries has declined dramatically in recent years.[8] The parasite is transmitted congenitally in 1–10% of pregnancies in women who are carriers,[9] posing an unavoidable risk for transmission in both endemic and non-endemic regions. Disease severity in neonates with congenitally acquired Chagas disease can range from asymptomatic acquisition[10] to fulminant disease culminating in death.[11] Ingestion of food or drink contaminated with trypomastigotes has recently been identified as the cause of several recent large-scale outbreaks of acute Chagas disease.[12,13] Other modes of transmission include organ transplantation[14] and laboratory accident.[15]

Acute chagas disease

Most patients with acute infection are asymptomatic or have mild symptoms. After an incubation period of 1–2 weeks, a minority of patients will experience a non-specific febrile illness. A newly infected individual may develop fever, chills, nausea, vomiting, diarrhea, rash, meningeal irritation, conjunctivitis, lymphadenopathy, or hepatosplenomegaly.[16] Acute infection may be accompanied by anemia, thrombocytopenia, or elevated liver enzymes. Blood form trypomastigotes can be observed in wet preparations of blood and cerebrospinal fluid (CSF) in many patients.[17] Eosinophilia is not associated with acute infection.[18] Serological tests for *T. cruzi*-specific antibodies can be negative during acute infection.[16] Although cardiac involvement in acute infection appears to be universal, myocarditis, cardiomegaly, and congestive heart failure only develop in a small percentage of acutely infected patients.[19] The presence of arrhythmias or bundle branch blocks portends a poor prognosis.[20] The mortality rate of acutely naturally infected patients, often children, is less than 2%, and the common mode of death is acute myocarditis or meningoencephalitis.[21]

There are several well-described dermatological manifestations of acute Chagas disease.

Chagoma

A chagoma is a red, indurated swelling at the site of inoculation,[22] which develops in the weeks after the initial bite and persists for weeks afterward. If a biopsy is obtained, pathology demonstrates intracellular amastigotes and lymphocytes.[23]

Romaña's sign

This classic sign of acute Chagas disease occurs due to the deposition of parasite-laden feces into the conjunctival sac. The patient may rub the eye after scratching at a freshly infected bite wound, transferring trypomastigotes to the conjunctiva. The patient subsequently develops eyelid edema and conjunctivitis, which may be associated with lymphadenitis or even pre-septal cellulitis.[24]

Schizotrypanides

A small minority of patients will develop a diffuse morbilliform eruption in the weeks after acute inoculation. Biopsy demonstrates dilation of the subpapillary plexus with swelling of the endothelial cells and edema of the surrounding connective tissue and lymphocytic perivascular infiltrates. Parasites are not present in the lesions.[23]

Indeterminate stage

In most patients, an immune response develops, the parasitemia wanes, and signs and symptoms resolve completely within a few months. These individuals then enter the indeterminate phase of infection, which is characterized by the presence of specific antibodies in the absence of clinical manifestations.[21] To be diagnosed with indeterminate stage disease, patients must demonstrate no clinical symptoms related to *T. cruzi* infection. Furthermore, electrocardiogram (ECG) testing and cardiac and gastrointestinal imaging must be normal. However, patients in the indeterminate stage remain parasitemic.[9] This phase may last from months to an entire lifetime.[21]

Chronic stage

Over a period of decades, 15–30% of patients with indeterminate stage Chagas disease will develop a chronic complication of *T. cruzi* infection, thereby progressing to the chronic stage of Chagas disease. The most common manifestations of chronic Chagas disease are cardiac and gastrointestinal.[22]

Chronic chagasic heart disease varies widely in its manifestations, ranging from asymptomatic ECG abnormalities to congestive heart failure, arrhythmias, and/or thromboembolic events.[25] The severity of the disease is dependent on the duration of illness as well as the location and nature of cardiac lesions.[26] Dilated congestive cardiomyopathy is an important manifestation and usually occurs years or even decades after a person first becomes infected. Apical aneurysm of the left ventricle is one of the hallmarks of chronic chagasic cardiomyopathy. The destruction of conduction tissue results in conduction abnormalities. The most common ECG abnormality is a right bundle branch block that may also be associated with an anterior fascicular block. A recently developed system for staging chagasic cardiac disease is presented in Table 1. Management of cardiac complications in patients with Chagas disease differs little from that in patients with cardiac problems from other causes.[25]

Gastrointestinal symptoms develop in 6% of patients with Chagas disease. The most common manifestations are those related to the megasyndrome. This results from damage to the autonomic ganglia leading to denervation of the tubular structures of the gastrointestinal tract. In the esophagus, this process leads to megaesophagus associated with achalasia. This is usually associated with dysphagia, weight loss, and characteristic radiological findings. These patients may also experience chronic aspiration. Management options are similar to those in idiopathic achalasia. Patients with megacolon due to denervation of the colon may experience constipation, which can be severe and unremitting. Management varies from

dietary changes and enemas in minor cases to surgical or endoscopic intervention in more severe cases.[27]

Reactivation

Patients with indeterminate or chronic Chagas disease who develop an immunocompromised state may experience reactivation of the infection. Reactivation syndromes may present as acute myocarditis or meningoencephalitis. Not uncommonly, however, patients present with fever and cutaneous lesions.[28] The cutaneous lesions are most commonly erythematous nodules or plaques. The diagnosis is made by visualizing intracellular amastigotes on pathology from skin biopsy specimens (Figs. 2-4). Reactivation with cutaneous manifestations has been described following kidney transplantation,[29,30] bone marrow transplantation,[28] cardiac transplantation,[31,32] and liver transplantation.[33] A similar presentation has been described in patients with HIV/AIDS.[3]

Epidemiology

The epidemiology of this disease has changed over the course of the last several decades. When initially discovered, Chagas disease was a disease endemic to the rural poor who lived in substandard housing, allowing close contiguity with the insect vector. Subsequently, blood transfusions became a major avenue of transmission of *T. cruzi* infection in major cities in endemic countries prior to the institution of blood donor screening.[4] The Southern Cone Initiative, supported by major international bodies, has significantly reduced the transmission of the infection through vector control programs.[21] Thus, Chile, Uruguay, and large portions of Brazil are now transmission-free, although it is worth noting that the gains achieved in Brazil have occurred despite the persistent presence of wild insect vectors capable of transmitting the parasite. In addition, there has been a decrease in the proportion of children in endemic countries who demonstrate antibodies against *T. cruzi*.[6] Nevertheless, an estimated 8 million[1] to 16-18 million[21] people worldwide have already been infected with *T. cruzi*, and cases of chronic reactivation and congenital Chagas disease will continue to present for decades. Caring for this cohort of infected people will remain a major challenge for Latin American countries due to economic and geographic barriers to the provision of health care to large proportions of this population. Furthermore, the United States, Europe, and Australia have seen large-scale immigration from Latin America in recent years. An estimated 325,671 immigrants in the USA are infected with *T. cruzi*, as are an estimated 86,947 in Spain, 5553 in Canada, and 3088 in Australia.[2] This cohort is at risk of developing the complications of chronic or reactivation Chagas disease while residing in countries where physicians are not familiar with this disease. Furthermore, although blood donor screening for Chagas disease has recently been instituted in the USA[8] and other countries with significant numbers of at-risk potential donors,[34] previous recipients of blood transfusions or organs in those countries remain at risk of developing Chagas disease, even without a history of travel to endemic areas. Furthermore, the vector is found in the southern USA, and several cases of natively acquired Chagas disease have been reported.[35] One study in Arizona, a state in which both Reduviid bugs and their sylvatic reservoir are plentiful, found that 41.5% of triatomine insects collected by volunteers demonstrated polymerase chain reaction (PCR) evidence of active *T. cruzi* infection.[36]

Laboratory diagnosis

The diagnosis of acute *T. cruzi* infection is usually made by observing trypomastigotes in wet mounts of blood or CSF or in Giemsa-stained slides (Fig. 5).[4] Inoculation of blood into special media[37] or into mice[38] may be required, though these methods may not be useful in aiding management decisions in acutely infected patients because parasites may not be seen for several weeks. PCR technology is thought to be the most sensitive method for detecting

acute and congenital infection.[39] If acute infection is suspected in an immunocompromised patient, an examination of tissue may be needed. Parasites may be observed in pericardial fluid,[40] bone marrow,[41] brain,[42] skin,[31] or lymph nodes.[43] The diagnosis of chronic Chagas disease is usually based on detecting specific antibodies. Several serological assays are employed, including indirect immunofluorescence (IFA) and enzyme-linked immunosorbent assay (ELISA). Serological assays are used widely for clinical diagnosis and screening donated blood, as well as in epidemiological studies. The diagnosis should only be made if antibody presence is confirmed with two different serological modalities or if one modality is used to confirm the presence of at least two antigens;[44] commercial kits combining multiple serological modalities or antigens have been developed.[45]

Treatment

The two established medications for the treatment of Chagas disease are benznidazole and nifurtimox, which are nitroheterocyclic compounds that have been available for decades. These drugs are only available in the USA from the Centers for Disease Control and Prevention. Benznidazole is the preferred agent due to its superior side effect profile and is given in doses of 5 mg/kg/d for 60 days.[46] Common side effects include rash (ranging from photosensitivity to severe exfoliative dermatitis), peripheral neuropathy, and bone marrow suppression. An initial complete blood count, hepatic function profile, and serum chemistries should be obtained upon initiation of treatment. Further complete blood counts should be obtained every two weeks while on therapy.[44]

Nifurtimox is given in dosages of 8–10 mg/kg/d in adults, 10–12.5 mg/kg/d in adolescents, and 15–20 mg/kg/d in children in four divided doses. The appropriate duration of therapy is 90–120 days.[46] The most common side effects are gastrointestinal and neurological (including mood changes and peripheral neuropathy). While on therapy, patients should be monitored with a complete blood count, hepatic function profile, and serum chemistries, initially, after 4–6 weeks of treatment, and upon completion. The patient's weight and the presence or absence of peripheral neuropathy should be noted every two weeks.[44]

Which patients benefit from pharmacological treatment remains the subject of clinical trials. Well-accepted indications include acute infection, congenital infection, infection of any stage in a child, accidental laboratory exposure, and reactivation in an immunocompromised host.[47] Although some studies have shown the potential for benefit in treating chronic or asymptomatic Chagas disease,[48] evidence for clear benefit is currently lacking.[49,50]

Conclusion

Chagas disease is a systemic infection of life-long duration that is of increasing global interest. Dermatologists should be aware of the acute signs and chronic manifestations of this disease. A high index of suspicion should be maintained for reactivation of this entity in immunosuppressed patients with an appropriate previous exposure history or a history of having lived in or traveled to an endemic area.

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Questions (See answers on page 508)

1. According to current expert consensus, which patient should definitely receive anti-Chagas therapy?
    - **a.** A 42-year-old asymptomatic man from Honduras identified as seropositive during a blood drive
    - **b.** A 65-year-old female from Brazil with end-stage Chagas cardiomyopathy
    - **c.** A 40-year-old female from Mexico with acute leukemia and positive Chagas serology
    - **d.** A 45-year-old phlebotomist with accidental exposure to T. cruzi-infected blood
2. During nifurtimox therapy, one should monitor the patient's physical exam for the development of which of the following?
    - **a.** Peripheral neuropathy
    - **b.** Hypopigmented macules
    - **c.** Pulmonary edema
    - **d.** Icterus
3. Which of the following has been identified as the cause of recent large-scale outbreaks of acute Chagas disease in Latin America?
    - **a.** Blood transfusions
    - **b.** Contaminated food or drink
    - **c.** Invasions by the insect vector into non-native habitat
    - **d.** Fecal–oral transmission
4. Which of the following laboratory abnormalities is NOT typical of acute Chagas disease?
    - **a.** Anemia
    - **b.** Thrombocytopenia
    - **c.** Elevated liver enzymes
    - **d.** Eosinophilia
5. Which of the following findings conveys the worst prognosis in acute Chagas disease?
    - **a.** The presence of trypanosomes in CSF obtained via lumbar puncture
    - **b.** A new bundle branch block on ECG
    - **c.** The presence of a chagoma on the right arm
    - **d.** Fever
6. What proportion of patients with positive T. cruzi serologies but no symptoms will progress to symptomatic chronic Chagas disease?
    - **a.** 0–10%

b. 15–30%

c. 40–60%

d. 80–100%

7. Which of the following is NOT an appropriate method to use in a patient with suspected acute Chagas disease?

a. Serological testing

b. Direct smear

c. PCR

d. Inoculation into mice

8. Which of the following patients meets diagnostic criteria for indeterminate Chagas disease?

a. A 45-year-old man from Bolivia with no symptoms, a right bundle branch block on ECG, and both a positive T. cruzi IFA and positive ELISA

b. A 40-year-old woman from Paraguay who reports developing Romaña's sign as a child and now has developed refractory constipation

c. A 60-year-old male from Brazil with no symptoms, normal ECG, and both a positive T. cruzi IFA and positive ELISA

d. A 50-year-old man from Venezuela with both a positive T. cruzi IFA and positive ELISA with newly-diagnosed dilated cardiomyopathy

9. A 40-year-old male from rural Guatemala develops fevers and several erythematous nodules several months after liver transplantation. Which of the following would be the most appropriate method to evaluate for reactivation Chagas disease?

a. Serum ELISA

b. Serum PCR

c. Skin biopsy for pathology

d. Inoculation of blood into mice

10. A 40-year-old Caucasian male in the USA develops biopsy-proven cutaneous reactivation of Chagas disease after undergoing renal transplantation. Which of the following would NOT be a possible method of his having contracted the disease?

a. Receipt of a blood transfusion 15 years previously

b. Exposure to Reduviid bugs as a child in rural Tennessee

c. Consumption of raw guava juice during a previous trip to Brazil 20 years previously

d. Sexual contact with a woman who subsequently developed Chagas cardiomyopathy

Answers to questions

1. d.

2. a.
3. b.
4. d.
5. b.
6. b.
7. a.
8. c.
9. c.
10. d.

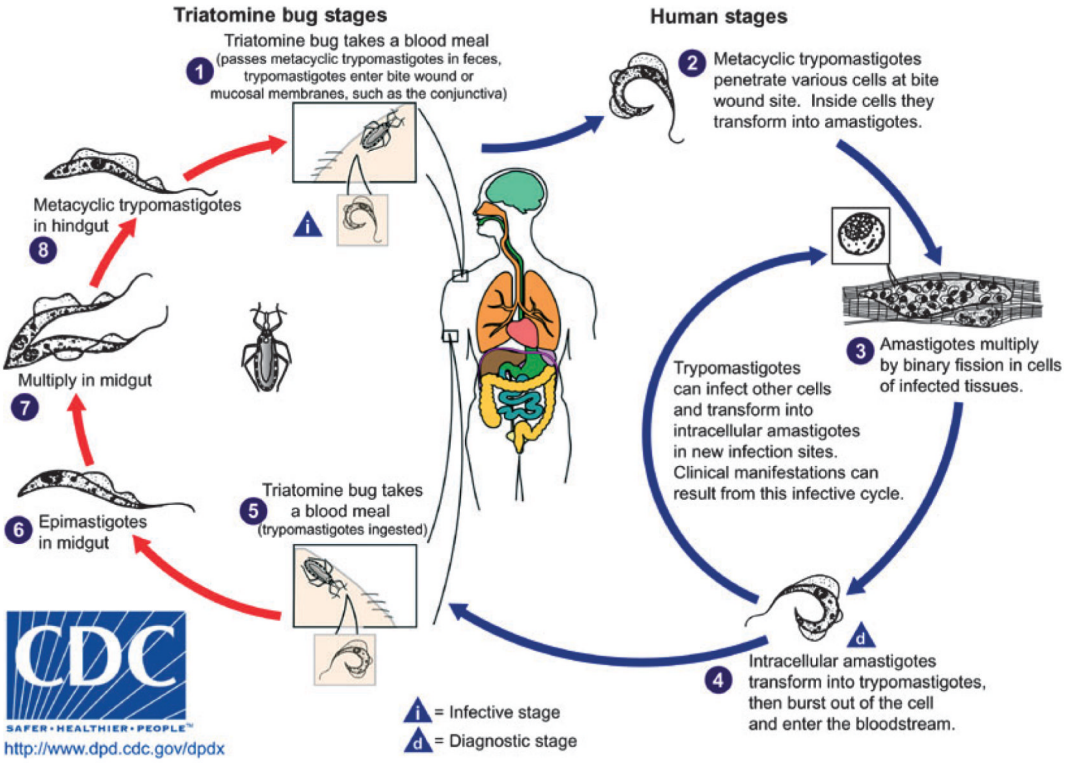

Figure 1.

The triatomine and human stages of the life cycle of *Trypanosoma cruzi* (courtesy of CDC)

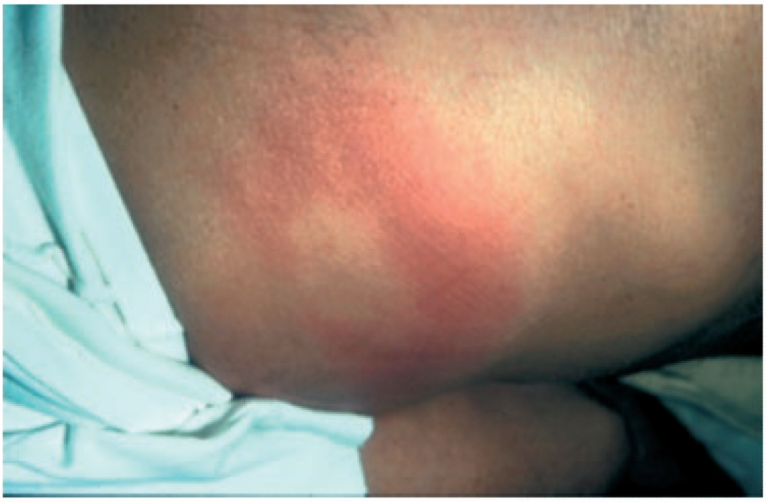

Figure 2.
Erythematous plaque in a renal transplantation patient with reactivation Chagas disease (Gallerano, 2007)

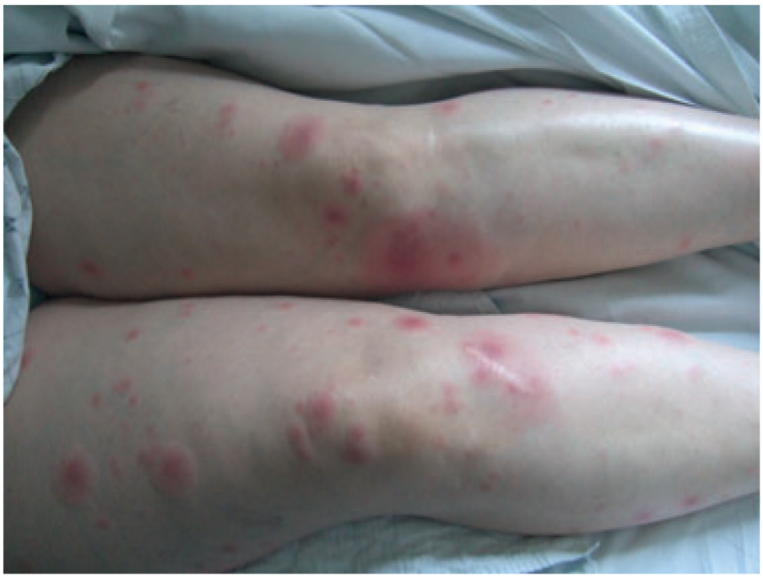

Figure 3.
Lower extremity plaques in a cardiac transplantation patient with reactivation Chagas disease in North America (courtesy of Eva Parker)

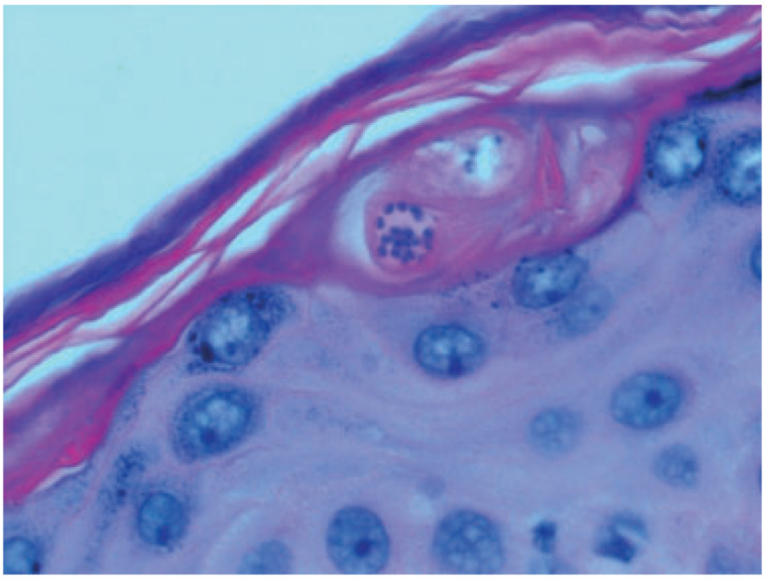

Figure 4.
Intracellular amastigotes visualized on an H&E stain from a skin biopsy specimen from the patient in Fig. 3 (courtesy of Eva Parker)

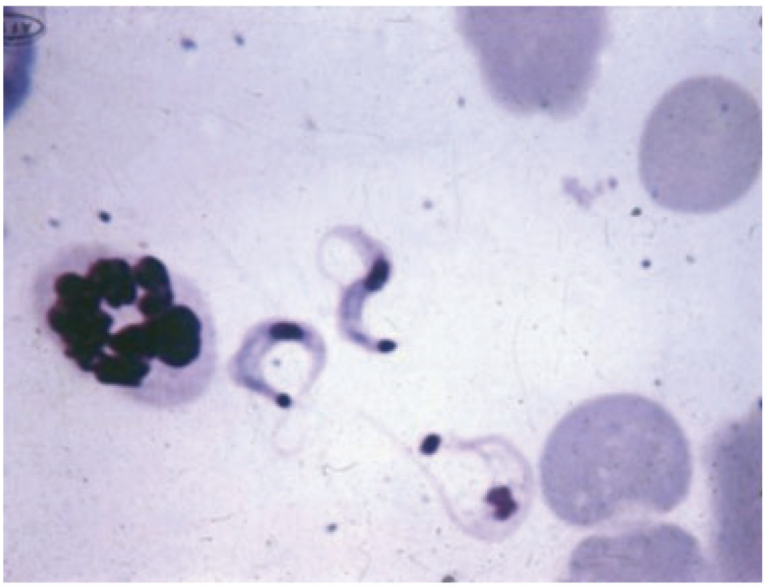

Figure 5.
Trypomastigotes in a Giemsa smear (×650) prepared from the blood of an infected mouse

Table 1

Staging of chagasic cardiomyopathy, according to the Brazilian Expert Consensus in Chagas disease

Stage	ECG	Echocardiogram	Symptomatic heart failure
A	Abnormal	Normal	Absent
B1	Abnormal	Abnormal Left ventricular ejection fraction >45%	Absent
B2	Abnormal	Abnormal Left ventricular ejection fraction <45%	Absent
C	Abnormal	Abnormal	Treatable
D	Abnormal	Abnormal	Refractory

ECG, electrocardiogram