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Special Article

Cardiac Manifestations of Parasitic Infections Part 2: Parasitic Myocardial Disease

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Summary

This is part two of a three-part series discussing parasites of the heart. In this section, we present an overview on parasitic diseases predominantly involving the myocardium.

Key words: heart, parasites, Chagas disease, pericardium, myocardium

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Parasitic Myocardial Disease

Toxoplasmosis

Humans become infected with *Toxoplasma gondii* (*T. gondii*) either by eating undercooked infected beef or pork, fecal-oral transmission from feline feces, organ transplantation, blood transfusion, or transplacental transmission.[1–8] The clinical expression of toxoplasmosis depends on the level of immunity in the human host.[1–4] In immunocompetent patients, toxoplasmosis can be asymptomatic, or presents in 10–20% of cases as a mononucleosis-like illness.[1,2] Latent infection is due to cyst formation that subsequently reactivates in immunocompromised persons.[1,8–14] Among these populations, toxoplasmosis often presents in the form of encephalitis or chorioretinitis.[1,8,9]

Myocarditis, pericardial effusion, constrictive pericarditis, arrhythmias and congestive heart failure have been described in patients infected with *T. gondii*.[5,6,10] In patients with the acquired immunodeficiency syndrome (AIDS), the heart is the second most commonly affected organ after the brain.[1,10,12] Prevalence varies according to various studies, and diagnosis is usually made postmortem since cardiac involvement is usually clinically silent.[10,12] Approximately 12—22% of AIDS patients had evidence of endomyocardial involvement by *T. gondii* at autopsy.[10–12] Prevalence of cardiac toxoplasmosis confirmed at autopsy in the highly active antiretroviral era has been reported to be less than 10%.[1,10–12] *T. gondii* associated myocarditis can also occur in transplant patients either due to a reactivation or to *de novo* infection from a seropositive donor to a seronegative recipient.[4,7–9] Indeed, toxoplasmosis is the most commonly reported parasitic disease occurring after heart transplantation.[5] Disseminated toxoplasmosis with associated myocarditis can lead to a fatal outcome if no prior prophylaxis is given in transplant patients.[11,14] The diagnosis of toxoplasmosis relies on serology or identification of the bradyzoites in myocardial tissue.[1,8,10,14]

The treatment of choice is based on a combination of pyrimethamine and sulfadiazine or pyrimethamine and clindamycin.[1,11]

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Trichinellosis

Trichinellosis is caused by *Trichinella spiralis* (*T. spiralis*) and has a worldwide distribution. Humans become infected when eating undercooked contaminated meat.[15–17]

The clinical picture of trichinellosis is directly related to the number of larva ingested and manifesting with two clinical stages: the intestinal stage and the muscular stage.[15–17] Larval migration into the muscles can cause periorbital and facial edema, subungal, conjunctival and retinal hemorrhages, myalgias, weakness, and fever.[18–20] The tropism of *T. spiralis* for striated muscle may lead to involving the myocardium in 21–75% of infected patients.[18,19] Complications such as cardiac arrhythmias are considered the most common cause of death associated with trichinellosis.[19,20] *T. spiralis* associated myocarditis is not caused by the direct larval invasion of the myocardium with encystation but is likely induced by an eosinophilic-enriched inflammatory response resulting in eosinophilic myocarditis similar to the pathogenic process associated with tropical endomyocardial fibrosis.[18–20] In addition, pericardial effusions have also been reported during *T. spiralis infection.*[18] The clinical suspicion of trichinellosis is based on the epidemiology associated with the typical clinical presentation and the presence of eosinophilia; confirmation is based on serology and muscle biopsy.[15,16] Electrocardiographic findings are considered nonspecific. According to a large study which included 560 patients, 59 had myocardial damage with two-thirds manifesting repolarization disturbances and one-third presented depolarization disturbances.[19,20]

Treatment consists of the administration of albendazole or mebendazole in conjunction with steroids for severe cases.[15–19]

Chagas' Disease

Trypanosoma cruzi (*T. cruzi*) is an obligate intracellular parasite that causes American trypanosomiasis or Chagas' disease, a chronic and debilitating parasitic infection that affects millions of people in Latin America and is increasingly reported in nonendemic settings due to reactivation among immigrant populations.[21,22] Approximately 25% of the population living in Latin America lives at risk of acquiring the infection.[21] The hematophagous reduviidae bugs responsible for transmitting *T. cruzi* to humans usually live in cracks and crevices of poor quality houses in rural areas (Fig. 1).[21,22] These insects emerge at night to bite and suck blood. The feces of these insects contain vast amounts of *T. cruzi*, which can enter the wound left after the blood meal, usually when it is scratched or rubbed.[21,22] In addition, Chagas' disease can also be transmitted through blood transfusions, transplants, or perinatally.[23–26] Recently, an outbreak of foodborne Chagas' disease in Brazil showed another form of transmission.[27]

The pathogenesis of myocarditis and subsequent myocardial dysfunction during *T. cruzi* infection is still a matter of intense debate. It has been postulated that a repetitive inflammatory response resulting in progressive neuronal damage, microcirculatory alterations and heart matrix deformation are the main pathogenic features in Chagas cardiomyopathy.[28–30] However, recent evidence has suggested that the chronic chagasic cardiomyopathy appears to be a continuous process associated with the persistence of the parasites in the myocardium.[21,28,29] Despite the demonstration of a low number of parasites during the chronic phases of Chagas cardiomyopathy, both polymerase chain (PCR)-based assays, and histological analysis have confirmed the presence of amastigotes

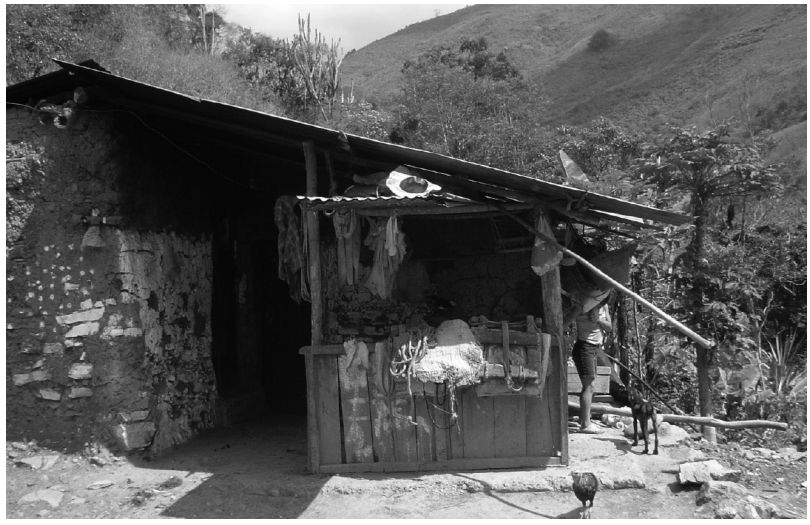

FIG. 1 Human dwellings conducive for transmission of Chagas' disease in endemic areas (rural area in Venezuela).

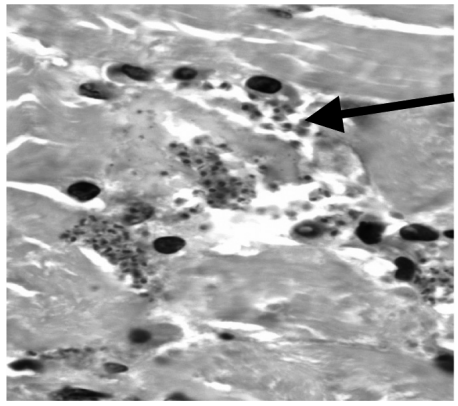

FIG. 2 *Trypanosoma cruzi* amastigotes (arrow) in the myocardium in the mouse animal model of Chagas disease cardiomyopathy.

in these patients possibly leading to irreversible long-term consequences of the megasyndromes or chagasic cardiomyopathy[28–31] (Fig. 2). These findings are further supported by the frequent reactivation of Chagas' disease among HIV-infected individuals.[1] Therefore, there is a growing consensus that elimination of *T. cruzi* in myocardial tissue is a prerequisite to halt the progression of the disease.[21,28,29] Furthermore, a role for parasite genetic variability in the spectrum of clinical disease associated with Chagas' disease is emerging. *T. cruzi* has been divided into two highly divergent genetic subgroups, lineages 1 and 2, isolated from humans, insect vectors, and sylvatic mammals.[30] The evolutionary origin of these two lineages and the clinical importance of their identification have been the subject of intense debate.[21,29,30]

The initial descriptions of the cardiac involvement in Chagas disease were completed by Carlos Chagas in the early 20th century.[22] In his early descriptions, he eloquently described the occurrence of significant cardiac conduction abnormalities, arrhythmias, and sudden cardiac death in his patients.[22] We now recognize that Chagas' disease has three different clinical stages. The acute stage follows the entry and invasion of the bloodstream by the protozoan parasite.[1,21–23] After the acute phase, the infected individual enters the chronic stage, which has a variable duration usually more than 10 or 20 years. At its end, the disease may follow three different paths: (i) development of megasyndromes; (ii) myocarditis with associated fibrosis which is considered the terminal form with highest mortality; (iii) or individuals may remain asymptomatic for the rest of their lives.[1,32] The cardiomyopathy associated with Chagas disease manifests as a biventricular failure with both systolic and diastolic dysfunction and associated cardiac arrhythmias or sudden cardiac death.[1,32] Sudden cardiac death accounts for 55–65% of deaths in Chagas' disease.[1,33,34] Pulmonary or systemic embolism arising from mural thrombi in dilated cardiac chambers may be identified at autopsies of patients who died of Chagas' disease.[34] Chagas' disease has become an important opportunistic infection among patients with HIV-infection or other types of immunosuppression such as organ transplantation causing reactivation of chronic latent *T. cruzi* infection and manifested as myocarditis or meningoencephalitis.[1]

The diagnosis of *T. cruzi* infection is made by epidemiological, clinical and serological criteria.[35–38] ECG findings are numerous but consist mainly of bundle-branch blocks and various degrees of atrioventricular blocks (Fig. 3).[35,36] Echocardiograms may reveal apical aneurysms, segmental wall motion abnormalities or diffuse hypokinesis.[35,36] Brain natriuretic peptide measurements could be a useful method to screen patients with Chagas' disease.[38]

Treatment of Chagas' disease is directed at both eradicating the parasite and targeting the cardiac manifestations of the disease.[1,21,32,39,40] Benznidazole and nifurtimox are used in the acute phase and in reactivation under immunosuppressive conditions.[1,21,32] Chemotherapy can shorten the acute phase and achieve a parasitological cure in 50% of the cases but causes significant toxicity.[1,21,32] However, there is no evidence that drug treatment of persons in the chronic phase can alter the natural history of the disorder.[32,39,40] There are many new compounds being considered that have discernible activity against *T. cruzi,* which appear to have better safety profiles and efficacy.[21]

Heart failure and arrhythmias in Chagas'disease are treated similar to other etiologies of heart failure.[1,32] Cardiac transplantation has been successfully performed in selected patients and survival was better compared to patients transplanted for other types of cardiac disease.[41] Results from dynamic cardioplasty and partial ventriculectomy are controversial.[42] Patients at high risk of sudden death can benefit from implantable cardioverter-defibrillator.[43]

African Trypanosomiasis

There are two forms of African trypanosomiasis: the West African form caused by *T. brucei gambiense* (*T. b. gambiense*) and the East African form caused by *T. brucei rhodesiense* (*T. b. rhodesiense*).[44–46] Both subspecies are indistinguishable but cause diseases that differ in their epidemiology, clinical presentation, and prognosis.[45,46] Humans are infected after they are bitten by a tsetse fly. Travelers can become exposed to African trypanosomiasis during safari trips.[44]

African trypanosomiasis manifests in three clinical stages.[46,47] The first stage is characterized by a painful chancre at the site of the inoculation followed by a Hemolymphatic stage, and subsequently to a third stage of meningoencephalitis. Infection with *T. b. gambiense* is a slowly progressive infection where no symptoms can be noted for months to years.[44–46] In contrast,

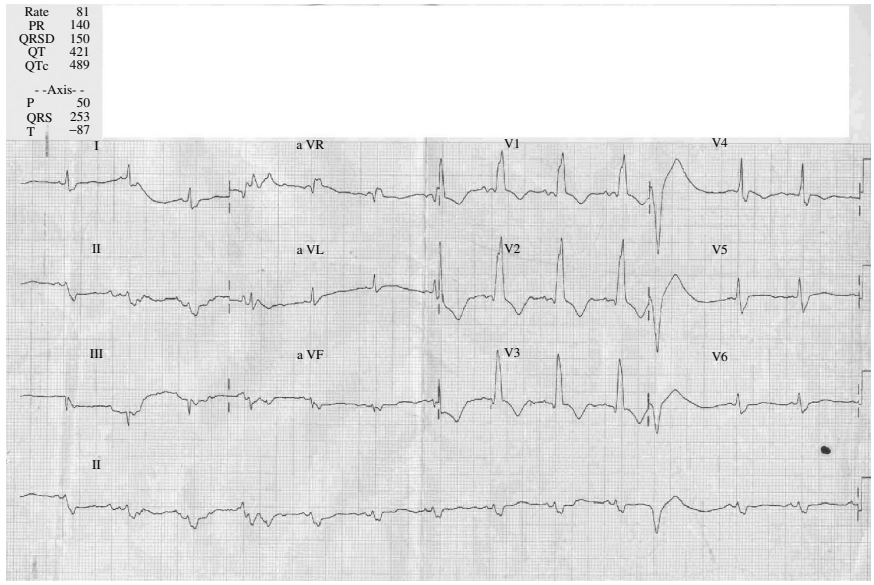

FIG. 3 Electrocardiogram from a patient with Dilated Cardiomyopathy due to Chagas' disease in Venezuela showing a complicated right bundle branch block ** and premature ventricular complexes. ** The conduction abnormality is considered to be complicated because the duration of the QRS interval is greater than 0.12 s, the mean QRS vector is directed at least—170° in the frontal plane and more than 50° anteriorly; and there is a primary T wave abnormality. This type of EKG tracing is commonly seen in various types of cardiomyopathy not exclusive of Chagas' disease.

T. b. rhodesiense infection tends to progress rapidly to the third stage of involvement.[45–48]

Myocarditis, with occasional pancarditis may occasionally develop during the hemolymphatic stage, leading to arrhythmias and heart failure with *T. b. rhodesiense* infection.[45–48] The pathophysiology of cardiac involvement in African trypanosomiasis is secondary to endarteritis and fibrosis caused by perivascular infiltration by trypanosomes and lymphocytes.[46,47] ECG abnormalities are present in half the cases sometimes manifested as cardiac conduction delays. A chest radiograph may show cardiomegaly and echography can identify ventricular dilatation and/or pericardial thickening.[45–48] Diagnosis is made by visualization of the trypanosomes from chancre fluid, lymph node aspirates, blood or cerebrospinal fluid.[44,46,47] Choices for treatment of African trypanosomiasis depend on the type of trypanosomiasis and on the clinical stage.[45,46]

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