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Natural Chagas Disease in Four Baboons

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Abstract

Background—Chagas disease is common in Central and South America and the southern United States. The causative agent is *Trypanosoma cruzi* (*T cruzi*, Order Kinetoplastida, Family Trypanosomatidae), a kinetoplastid protozoan parasite of humans and other vertebrates. It is a serious public health issue and the leading cause of heart disease and cardiovascular death in Central and South America. In 1984 a colony baboon was discovered to be infected with *T cruzi*.

Methods—Since the initial diagnosis was made by microscopic observation of the amastigote forms of *T. cruzi* in myocardial fibers, *T. cruzi* amastigotes have been identified in three additional baboons.

Results—The primary findings were similar in all four baboons and were congestive heart failure with edema of dependent areas, hydrothorax, hydropericardium, and multifocal to diffuse lymphoplasmacytic myocarditis.

Conclusions—A baboon animal model of Chagas disease could contribute significantly to the development of therapies for the disease in humans.

Keywords

nonhuman primate; protozoa; animal model; heart; *Trypanosoma cruzi*

Introduction

Chagas disease (*American trypanosomiasis*) (11,12) is a zoonotic disease common in Central and South America and the southern United States (29,60). The causative agent of Chagas disease is *Trypanosoma cruzi* (*T cruzi*, Order *Kinetoplastida*, Family *Trypanosomatidae*), a kinetoplastid protozoan parasite of humans and other vertebrates.

Chagas disease is a serious public health issue—it is the leading cause of heart disease and cardiovascular death in Central and South America (24,29,30,47,52), and only malaria and schistosomiasis pose greater tropical disease burdens (61). The disease is estimated to affect 16–18 million people in Latin America, and 120 million people are at risk of becoming infected (62). About 27% of those infected will develop cardiac symptoms, and 9% of cases progress to gastrointestinal or peripheral nervous system involvement (60). There are no vaccines to prevent infection, and no safe and effective therapeutic options (15,19,42,55,56,57). Serious concerns have been raised about the safety of domestic blood

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and tissue banks, and the risk of transfusion- and transplant-associated transmission of Chagas disease, as the number of infected individuals migrating to the US increases (10,13,23,25,36,45,46,49,50).

A number of cases of Chagas disease in humans and other animals have been reported in the United States, particularly in the south and especially in southern Texas and Louisiana (1,4,5,6,9,13,17,18,24,39,41). Natural (53) and experimental (40) *T. cruzi* infection has also been documented in multiple New World and Old World primate species. In 1984 a baboon from the outdoor primate colony at the Southwest National Primate Research Center at the Southwest Foundation for Biomedical Research (SPC) in San Antonio, TX, was found dead in its cage and subsequently determined to be infected with *T. cruzi* (21). Since this initial discovery, more than 182 baboons in the colony have tested seropositive for *T. cruzi*, and Chagas disease is now suspected in a number of baboon deaths. The primary route of infection has not been positively established, but in consequence of their largely outdoor housing the baboons are believed to become infected by catching and eating infected insects (2,3,14,33,48,54). Based on retrospectively collected data on seropositivity to *T. cruzi*, the seroprevalence in the baboon colony is currently estimated at 2–3%.

In this report we summarize the major pathologic and histologic findings in four cases of confirmed Chagas disease in colony baboons. These cases exhibit considerable similarity in their gross, microscopic, and histologic features and illustrate clearly the similarity of chagasic pathology in baboon to that seen in human cases of the disease.

Parasite Cycle and Morphology

The most common mode of transmission of Chagas disease is via several hematophagous species of triatomine (reduviid) insect (Order *Reduviidae*, Family *Hemiptera*). Following a blood meal the insect defecates near the site of the bite, and the human host can become infected when the feces from a parasitized insect contaminate the bite wound or penetrate the body through broken skin or the mucosa of the mouth and eyes. Infection can also result from eating infected insects, and is probably a significant route of infection in nonhuman vertebrates such as the opossum and domestic dogs (3,14,33,48,54).

T. cruzi epimastigotes replicate in the gut of the insect vector and differentiate into metacyclic trypomastigotes. These are released with the feces of infected insects and enter the host through broken skin or mucosal membranes. The trypomastigotes appear in blood stains as long, slender, C– or S–shaped flagellates 15–20 μm in length. A single flagellum originates posteriorly, travels superiorly along the spindle-shaped body of the organism, and projects anteriorly as free flagellum (16,20,37). Trypomastigotes invade a variety of tissues in the vertebrate host and replicate as amastigotes, which are smaller, ovoid, aflagellate forms 2–5 μm in length. These proliferate intracellularly before differentiating into a variant form of trypomastigote and entering the bloodstream to infect additional cells, or to be taken up by another insect vector during a blood meal. In all forms a large, round central nucleus and a posteriorly located, elliptical- or bar-shaped kinetoplast are easily visualized (16,21).

Diagnosis of Chagas Disease

Microscopic detection of *T. cruzi* organisms in the blood or tissues of infected subjects has long been the gold standard for diagnosing Chagas disease (32). Although an animal may be seropositive for *T. cruzi*, or suggestive sub-clinical lymphocytic myocarditis may be observed histologically, direct observation of the infectious organism in the tissues is considered crucial for establishing that the cardiomyopathy is actually chagasic.

During the acute stage of infection, trypomastigotes can frequently be detected in the peripheral circulation and morphologic criteria for identifying the organisms as *T. cruzi* can be applied (8,37). Visual identification of the parasite is greatly facilitated by the presence of the central nucleus and bar-shaped kinetoplast (16). Observation of the kinetoplast is considered diagnostic for *T. cruzi*, and aids in differentiating *T. cruzi* from the morphologically similar intracellular protozoa *Sarcocystis spp*. and *Toxoplasma spp*. (27,38).

In the intermediate and chronic stages of the disease the trypomastigotes effectively disappear from the peripheral circulation and are extremely difficult to detect microscopically. Ideally, sectioning of infected tissues will reveal intracellular nests of kinetoplastid amastigotes, otherwise positive determination of infection with *T. cruzi* generally requires the application of several diagnostic techniques, such as microscopic examination of blood smears, serological assays, xenodiagnosis, and PCR-based assays for direct detection and quantification of parasite DNA (7,31,32,34,35,44).

Materials and Methods

The baboons described in this report were housed at the SPC in San Antonio, TX. SPC is located on a 332-acre campus in southern Texas and currently maintains a colony of about 3600–3700 baboons, as well as smaller numbers of primates such as chimpanzees, macaques, and marmosets. The colony was initiated in 1958 with founder baboons captured in the wild in Kenya and Tanzania (22,59), and the present colony comprises 5–6 generations of animals. Regular introduction of new, unrelated founder baboons helps to maintain or increase overall genetic diversity in the colony. Most of the baboons in the present colony are *P.h. anubis* (olive baboons), *P.h. cynocephalus* (yellow), and their hybrids, but there are also small numbers of *P.h. hamadryas* (sacred) and *P.h. ursinus* (Chacma).

All animals at SPC are cared for in strict compliance with the *Guide for the Care and Use of Laboratory Animals* [National Research Council, 1996], the *Animal Welfare Act*, and the *Institutional Animal Care and Use Committee* of the SPC.

Housing

Except as required for colony management or special projects, baboons are housed in large, multi-animal enclosures with some degree of outdoor exposure. About 300–700 baboons are maintained in each of two circular, 6-acre, open-air corrals having dirt floors and sheet-metal walls (22). The remaining baboons are mostly housed in various outdoor, but sheltered, gang-cage facilities having concrete floors and open walls of chain-linked fencing material. The baboons are fed a standard diet (SWF Primate Diet 3715; Harlan-Teklad, Madison, WI, USA) ad libitum.

Pathology

Complete necropsies were done on all the baboons and extensive tissue samples were collected, fixed in 10% neutral-buffered formalin, processed conventionally, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin (H & E). Standard techniques of light microscopy were used to search tissue sections for nests of the amastigote form of *T. cruzi*. A positive diagnosis of Chagas disease was made if any intra- or extracellular forms of the parasite could be microscopically visualized, and identified as *T. cruzi* according to morphological criteria.

Serology

Serum samples from three of the case report baboons were assessed for *T. cruzi* seropositivity. One of these animals had offspring; serum samples from all three offspring were also assessed for *T. cruzi* seropositivity. Seropositivity to T. cruzi was assessed using an in vitro enzyme immunoassay (EIA) for the qualitative detection of antibody to T. cruzi (Abbott Laboratories, Abbott Park, IL). This assay does not cross-react with the nonpathogenic trypanosome T. rangeli, which is transmitted by some of the same vectors as T. cruzi [38]. Additional serologic tests included Enzyme Linked Immunosorbent Assay (ELISA), using *T. cruzi* antibody; IVD Research, Inc., Carlsbad, CA, and Bio-Manguinhos, Ministry of Health, Oswaldo Cruz Foundation, Rio de Janeiro and Indirect Immunofluorescence Assay (IFA) (using immobilized *T. cruzi*), Bio-Manguinhos, Ministry of Health, Oswaldo Cruz Foundation, Rio de Janeiro.

Case Reports

Serodiagnostic and histopathologic data have shown that colony baboons at the SPC become infected with *T. cruzi* and develop clinically evident Chagas disease. Infected animals manifest a chronic-stage symptomatology and may eventually die from the disease, typically from congestive heart failure (43,58). A decisive diagnosis of Chagas disease, however, is frequently elusive. Among the colony animals that have tested seropositive for *T. cruzi* and are believed to be infected, blood smears have never revealed the extracellular trypomastigotes. In four exceptional cases, however, organisms morphologically consistent with *T. cruzi* were confidently identified in the heart tissues of the infected animals, pointing conclusively to a diagnosis of Chagas disease. All four cases died of spontaneous, natural causes between 1984 and 2002.

Case 1

This is the initial case of chagasic pathology recognized in the baboon colony at the SPC, and reported by Gleiser (21). A female *P.h. cynocephalus*, age 3.6 mo, was discovered dead in its cage. No external gross lesions were recognized. Findings included pleural effusions, ascites, lymphoplasmacytic myocarditis with occasional neutrophils, and Individual myofiber necrosis. Numerous amastigotic nests were seen in myocardial fibers and an inflammatory cell response was clearly associated with ruptured myofibers. Unfortunately, no archived blood or tissues from this animal are available for retrospective analysis.

Case 2

The animal was a male *P.h. anubis* aged 6.6 yr, that had been on and off its feed for several weeks. Following a natural death, fresh blood was noted around the mouth and perianal areas, and the posterior subcutaneous tissue of both thighs was markedly edematous. The thoracic and peritoneal cavities contained an excess of clear, reddish-brown fluid, and the pericardial sac contained similar clotted material. A chronic, diffuse, multifocal nonsuppurative inflammatory reaction was present in the heart. Inflammatory infiltrate comprising primarily lymphocytes and plasma cells was associated with fibrosis and necrotic myocardial fibers.

Clusters of elliptical organisms morphologically consistent with *T. cruzi* were observed in many myocardial fibers. Lymphocytic foci were present in esophageal skeletal muscle. Pulmonary vasculature was markedly congested and edematous, with a diffuse proteinaceous fluid accumulation in the alveolar spaces. The liver showed chronic passive congestion with severe centrilobular necrosis. Other changes included interstitial nephritis with lymphocytes and multifocal nephrocalcinosis. Also noted were lymphocytic infiltrates

of the smooth muscle and lamina propria in the urinary bladder wall. A blood sample collected at age 2.7 yr was seronegative for *T. Cruzi* by EIA.

Case 3

A female *P.h. anubis* aged 10.4 yr was discovered dead in a transfer cage following hospitalization for mastitis. Gross examination revealed a thick, white, plaque-like lesion on the heart left ventricle near the apex, sufficiently severe to have been the cause of death. Microscopically there were multifocal lymphoplasmacytic myocardial infiltrates with associated myocardial necrosis. The inflammation was especially prominent in the endocardium and left ventricle, and organisms morphologically consistent with *T. cruzi* were identified in a single cardiac muscle fiber. Other changes included lymphoplasmacytic cholangiohepatitis. A blood sample collected at age 5.2 yr was seronegative for *T. Cruzi* by both ELISA and IFA. This animal was dam to three viable offspring (2 F, 1 M), all of which have since died, but on the basis of the most recent sample from each (collected at ages 3.9, 10.2, and 11.5 yr), all offspring of this animal were seronegative for *T. Cruzi*, one by EIA and ELISA and the other two by EIA, ELISA and IFA.

Case 4

A male *P.h. anubis*/*P.h. cynocephalus* hybrid, aged 8.7 yr, presented with pitting edema and well-defined necrosis of the lower left leg. The left hand appeared paralyzed. Heart rate was elevated with a gallop rhythm. Hematuria and semenuria were noted, the scrotum was markedly distended, and the bladder contained a hypoechoic substance. The clinical signs were consistent with deep vein thrombosis or similar vascular obstruction, infarction, and septicemia, and the animal was euthanized.

Gross examination revealed thrombosis of the medial and distal portions of the femoral artery, with secondary degeneration and necrosis of the supported skeletal muscle. The right kidney was almost totally infarcted and necrotic. The lungs were massively congested with abundant dark eosinophilic proteinaceous material in alveolar spaces. Histologically the myocardium had focal to diffuse collections of mixed inflammatory infiltrates, and rare myofibers contained protozoal organisms consistent with *T. cruzi* (Figure 1). A blood sample collected at necropsy (8.7 yr) was seropositive for *T. cruzi* by EIA, ELISA and IFA.

Discussion

Since the initial case report of *T. cruzi* infection in a baboon at the SPC (21), three additional cases of Chagas disease in the baboon colony have been confirmed by microscopic visualization of the infectious organism, and in one case by serology. The new cases have many features in common with the index case, and collectively these four cases now define the clinical and histopathologic presentation of chagasic pathology in the baboon.

In each case, necropsy disclosed pathology consistent with Chagas disease, and organisms morphologically consistent with *T. cruzi* were identified microscopically. The primary findings were congestive heart failure with associated edema of dependent areas, severe multifocal to diffuse myocarditis, extensive lymphocytic and plasmacytic myocardial infiltration, hydrothorax and hydropericardium. Heart failure was indicated by the consistent association of chagasic pathology with congestion and necrosis of the liver and congestion and edema of the lung. All four cases were essentially identical with respect to *T. cruzi*-induced primary gross and histologic expression of the disease, and differed only in the severity of lesions.

The logistics of controlling the disease in a large outdoor baboon colony of nearly 4000 baboons is difficult. The best techniques are to establish a good vector control program, practice good managemant and clinical care, cull infected baboons and use therapy, as a last option, for valuable animals. Therapy is generally not practical, as it expensive and requires maintainence of individual animals in the hospital indefinitely and repeated sedation of an animals on a regular schedule for the administration of chemotherapeutic agents. Additionally, once an infected baboon has entered the chronic stage of the disease chemotherapy is generally ineffectual (15,19,28,51,55,56,57). Baboons that are seropositive for *T. cruzi* are monitored closely, however, and an extensive panel of tissue specimens is collected when any of these animals die. Special precautions against accidental infection (26) are taken when personnel must work with seropositive animals.

Our present understanding of Chagas disease in the colony baboons at SPC is derived entirely from retrospective data, and is therefore limited in various irremediable ways. There are many aspects of the disease process, from exposure to infection, seroconversion, and pathogenesis, that are not easily investigated with such data and will require dedicated prospective studies. Nevertheless, the concordance of chagasic pathology in baboons to that observed in humans suggests that the baboon can be developed as a nonhuman primate animal model for Chagas disease in humans (43,58). Baboons can become infected naturally with *T. cruzi*, and infected animals exhibit the disease progression and pathologic changes, including EEG abnormalities, seen in human cases of Chagas disease (63,64,65). In many cases the infected animals develop frank Chagas disease and die of cardiac-related causes. A nonhuman primate animal model with these features could contribute significantly to the development of therapies for Chagas disease in humans.

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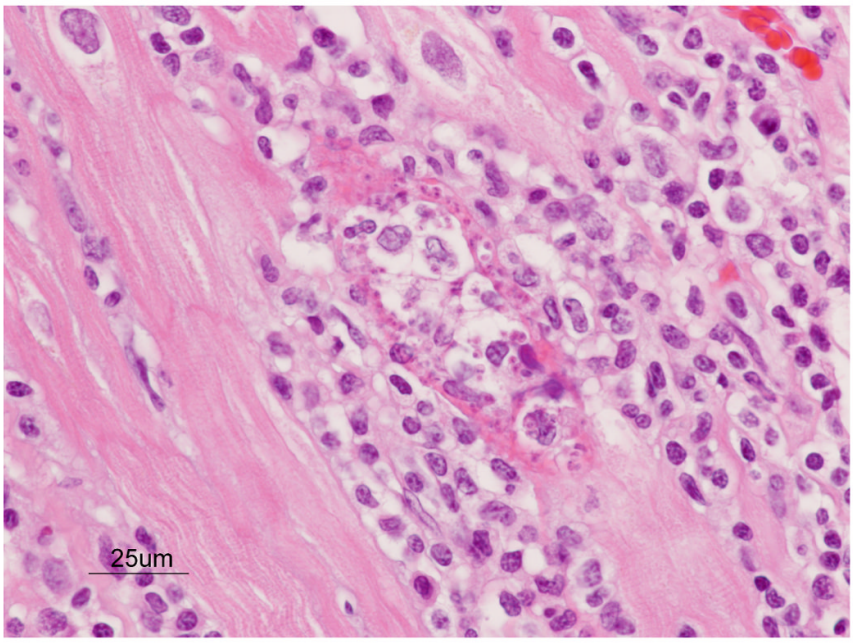

Figure 1.
Focal mononuclear inflammation and myocarditis in a nine year old male baboon. Note the lymphoplasmatic cell infiltrates, separation of myocardial fibers, necrosis, and nest of T. cruzi amastigotes within one myofiber. H&E stain.