REACTIVATION OF CHAGAS’ DISEASE IN A HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENT LEADING TO SEVERE HEART DISEASE WITH A LATE POSITIVE DIRECT MICROSCOPIC EXAMINATION OF THE BLOOD

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Abstract. We report a human immunodeficiency virus (HIV)—infected man with chronic Chagas’ disease who developed a congestive heart failure that could not be clinically controlled. Endomyocardial biopsy revealed severe myocarditis and the xenodiagnosis result was positive, but Trypanosoma cruzi by direct microscopic examination of the blood was found only four months after the symptoms had started. Treatment with benznidazole was effective in reducing parasitemia, stabilizing the clinical status, and controlling tissue damage related to the parasite. Although the finding of T. cruzi trypomastigotes by direct microscopic examination of the blood has been considered the mark of Chagas’ reactivation in immunocompromised patients with chronic disease, in this case it was a late finding.

Since 1990 there have been reports of reactivation of chronic Chagas’ disease in patients infected with human immunodeficiency virus (HIV).1–6 In these patients, Trypanosoma cruzi most commonly affects the central nervous system (CNS) with expansive lesions or meningoencephalitis.1–4 When the CNS is affected, the diagnosis of trypanosomiasis reactivation is clear because in immunocompetent patients with chronic Chagas’ disease CNS involvement is not observed.7

Cardiopathy during Chagas’ disease reactivation in HIV-infected patients has also been reported, usually associated with major CNS involvement.1,3,4 Heart disease as the main clinical manifestation of T. cruzi reactivation in HIV-infected patients has rarely been described.5 In these cases, it is very difficult to make a differential diagnosis between Chagas’ disease reactivation and severe chronic chagasic cardiopathy since the clinical manifestations are similar. Trypanosoma cruzi trypomastigotes observed by direct microscopic examination of the blood characterizes the acute phase of the disease and have been used to confirm Chagas’ disease reactivation.5 This is because during the chronic phase of the disease in immunocompetent patients, parasitemia can only be demonstrated by indirect methods (xenodiagnosis [in this procedure, insect vectors are fed blood from suspected patients and between 30 and 90 days after the blood meal, parasites are detected microscopically in the feces or intestines of the bugs], blood culture, or inoculation into experimental animals).

We have previously reported a case series of 18 patients with chronic Chagas’ disease and HIV infection, in which three cases of trypanosomiasis reactivation with cardiac manifestation occurred.6 In this paper, we report the follow-up of one patient who presented with severe heart disease caused by Chagas’ diseases reactivation. Treatment with benznidazole was effective in reducing parasitemia and controlling tissue damage.

CASE REPORT

A 36-year-old man had lived his first five years in an endemic area for vectorial transmission of Chagas’ disease in Brazil and then moved to the city of São Paulo, a non-endemic area where he had been living for 31 years. He was an intravenous drug user, had had sex with men, and had had an asymptomatic HIV infection since September 1988. In October 1994, his chest radiographs showed no abnormalities (Figure 1).

On February 4, 1995 he was admitted to the Infectious Diseases Clinic of the Hospital das Clínicas, a large teaching hospital affiliated with the University of São Paulo. During the previous eight months he had presented weight loss, malaise and thrush; during the last two months he developed congestive heart failure, which rapidly evolved to functional class IV.5 This could not be clinically controlled and led to his hospitalization. On physical examination, he showed signs of congestive heart failure.

Chest radiographs showed a significant global heart enlargement (Figure 2). A two-dimensional echocardiogram showed severe dysfunction and dilation of all cavities (end diastolic left ventricular diameter = 6.7 cm; end diastolic left ventricular volume = 301 ml; end systolic left ventricular diameter = 5.9 cm; end systolic left ventricular volume = 205 ml, left ventricular ejection fraction = 31%). An electrocardiogram (ECG) showed a right-bundle-branch block, left anterior-fascicular hemiblock, and isolated atrial and polymorphic ventricular extrasystoles. Test results for anti-HIV antibodies (ELISA and Western blot) were positive. His CD4 lymphocyte count was 826 cells/mm3 (20.7% of the total lymphocytes) and his CD8 lymphocyte count was 2,266 cells/mm3 (56.8% of the total lymphocytes). Chagas’ disease serologic test results were positive (indirect hemagglutination titer > 1:160 and indirect immunofluorescence titer = 1:160), and serologic results were negative for IgM antibodies to T. cruzi. Trypanosoma cruzi parasitemia was detected by xenodiagnosis and the proportion of positive bugs (64.1%) showed high parasitemia. However, at this time the blood cultures for T. cruzi (using 1 ml of blood on infusion tryptose medium) and the direct microscopic examination for trypomastigote forms of the parasite in the blood were negative. An endomyocardial biopsy was performed. The histologic examination of the endomyocardial fragments demonstrated a severe confluent lymphocytic in-
CHAGAS' DISEASE AND HIV INFECTION

Figure 1. Normal chest radiograph of the patient in October 1994.

Figure 2. Chest radiograph of the patient in February 1995 showing a significant global heart enlargement.

Figure 3. Histologic section of the first endomyocardial biopsy of the patient demonstrating severe confluent lymphocytic inflammatory infiltrate replacing the myocardium (hematoxylin and eosin stained, original magnification × 315).

Inflammatory infiltrate with some eosinophils, associated with myocyte degeneration and necrosis. There were also mild replacement fibrosis and myocyte hypertrophy (Figure 3). According to the Dallas criteria, the final diagnosis was severe confluent lymphocytic myocarditis with mild replacement fibrosis.

On March 1995, the blood cultures for *T. cruzi* became positive (two samples), and on April 27, 1995 trypomastigote forms were observed by direct microscopic examination of the blood (quantitative buffy coat method). At this time, his ECG showed the previously described alterations and ventricular bygeminism.

Reactivation of Chagas’ disease causing severe heart disease was diagnosed based on the clinical course, the endomyocardial histologic examination, and the finding of trypomastigote forms by direct microscopic examination of the blood. On May 4th, 1995 therapy for infection with *T. cruzi* with benznidazole (6 mg/kg/day) was started. The patient was treated for 90 days with clinical improvement, and stabilized in functional class II heart failure. At the end of the treatment with benznidazole he presented with leukopenia (3,800 cells/mm³) and thrombocytopenia (60,000 cells/mm³). His CD4 lymphocyte count was 325 cells/mm³ (30% of the total lymphocyte count) and his CD8 lymphocyte count was 521 cells/mm³ (48% of the total lymphocyte count). After treatment with benznidazole was stopped, the leukopenia improved, but the thrombocytopenia persisted. When anti-retroviral therapy with zidovudine was started, the platelet count increased.

Results of xenodiagnosis, blood cultures for *T. cruzi*, and direct microscopic examination of the blood became negative on the 14th day of treatment with benznidazole and remained so after treatment (seven samples in 10 months). Chagas’ disease serology remained positive and there were no significant alterations in antibody titers.

Nine months later his Echocardiogram showed a right-bundle-branch block and left-anterior-fascicular hemiblock, without arrhythmia, and a two-dimensional ECG showed similar cavity dimensions. Fourteen months after the first biopsy, a second endomyocardial biopsy showed moderate myocyte hypertrophy. There was no inflammatory infiltrate, cardiomyocyte damage, or interstitial fibrosis (Figure 4). The final diagnosis was resolved (healed) myocarditis.

**DISCUSSION**

In this case, the patient could not have experienced an acute *T. cruzi* infection since he had not recently been in an area endemic for the disease, and had not received blood transfusions. Since he had not previously been subjected to laboratory investigations for Chagas’ disease, but was originally from an endemic area, it is probable that he had acquired Chagas’ disease during his childhood, and that the HIV-related immunosuppression led to trypanosomiasis’ reactivation.

The patient, previously asymptomatic, presented with con-
gestive heart failure that rapidly evolved to functional class IV. High *T. cruzi* parasitemia was demonstrated by xenodiagnosis. Endomyocardial biopsy showed severe myocarditis that resolved with specific anti-*T. cruzi* treatment. However, the finding of trypomastigote forms of the parasite by direct microscopic examination of the blood occurred only four months after the symptoms had started, two months after high parasitemia had been demonstrated by xenodiagnosis, and 45 days after the endomyocardial biopsy that led to the histologic diagnosis. Although the finding of *T. cruzi* trypomastigotes by direct microscopic examination of the blood has been considered the mark of Chagas’ disease reactivation in patients with chronic disease, in this case it was a late finding.

The reactivation process is probably due to an imbalance of the delicate relationship between the parasite and the host that occurs when the host’s cellular immune system is affected. The immunosuppression allows *T. cruzi* to escape control mechanisms, resulting in parasite multiplication, enhancement of tissue inflammation, and high parasitemia. During this process, the parasitemia is probably escalating and in the early stages may only be detected by indirect methods such as xenodiagnosis and blood cultures.

Treatment of *T. cruzi* infection with benznidazole was effective in reducing parasitemia, stabilizing the clinical status, and controlling tissue damage related to the parasite, as shown by the second endomyocardial biopsy. Other investigators also reported successful treatment of Chagas’ disease reactivation. It is not yet clear which criteria may be used to indicate the need for treatment of *T. cruzi* infection in immunocompromised patients with chronic Chagas’ disease. When unusual clinical or laboratory manifestations, such as meningoencephalitis or detection of *T. cruzi* by direct microscopic examination of the blood or cerebrospinal fluid occur, treatment is mandatory. However, CNS involvement is not always present in Chagas’ disease reactivation and the detection of *T. cruzi* trypomastigotes by direct microscopic examination of the blood may be a late finding. The histologic diagnosis of reactivation is not clear, and endomyocardial biopsy is an invasive procedure not possible in all cases. Treatment should be started in the early stages of the reactivation process when irreversible alterations have not occurred. The follow-up of this case suggests that treatment may be considered for immunocompromised patients with high parasitemia even if it is detected by indirect methods.

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