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Case Report

Chagas disease (*Trypanosoma cruzi*) and HIV co-infection in Colombia

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SUMMARY

Chagas disease is a complex zoonotic pathology caused by the kinetoplastid *Trypanosoma cruzi*. This parasite presents remarkable genetic variability and has been grouped into six discrete typing units (DTUs). The association between the DTUs and clinical outcome remains unknown. Chagas disease and co-infection with HIV/AIDS has been reported widely in Brazil and Argentina. Herein, we present the molecular analyses from a Chagas disease patient with HIV/AIDS co-infection in Colombia who presented severe cardiomyopathy, pleural effusion, and central nervous system involvement. A mixed infection by *T. cruzi* genotypes was detected. We suggest including *T. cruzi* in the list of opportunistic pathogens for the management of HIV patients in Colombia. The epidemiological implications of this finding are discussed.

1. Introduction

Chagas disease is a complex zoonosis caused by the protozoan *Trypanosoma cruzi*. This pathology is considered a public health problem in South America where 7.7 to 10 million people are infected. Currently, Chagas disease is expanding to other continents, such as Australia, Europe, and North America, and is becoming a serious issue in non-endemic countries.[1] The co-infection of Chagas disease and HIV/AIDS has been documented widely. Most co-infected patients acquire *T. cruzi* through the vector-borne route in childhood and acquire HIV later in life. It is estimated that 98% of co-infection cases are diagnosed in the chronic stage of the disease, in a context of reactivation, while the remaining 2% are associated with acute infection.[2] According to previous studies, the most important clinical manifestations of Chagas disease with HIV/AIDS are associated with the central nervous system (CNS) (74.2% of cases), probably as result of severe immunosuppression that gives rise to the primary clinical manifestation of meningoencephalitis. A second category of clinical manifestations is associated with chagasic cardiomyopathy, which is more rare (16.7% of cases) and generally gives rise to the clinical manifestations of heart failure and arrhythmia.[2]

T. cruzi displays a relevant genetic variability demonstrated by at least six discrete typing units (DTUs) from TcI to TcVI.[3] Evidence of the impact of this genetic variability on HIV co-infection is scarce. However, some studies have suggested a differential tissue tropism of the infecting DTUs; these studies have reported mixed infections in co-infected patients, observing TcI and TcII, or TcI, TcV, and TcVI in blood, and only monoclonal TcI in cerebrospinal fluid (CSF) or brain tissue.[4] Herein, we detected and typed *T. cruzi* DTUs from heart and brain tissue of a Chagas disease patient with HIV/AIDS co-infection who presented severe cardiomyopathy and encephalopathy.

2. Case report

A 34-year-old female with an HIV infection (confirmed by Western blot) who was not receiving antiretroviral treatment, was hospitalized in March 2012. The patient reported having experienced 25 days of evolving chest pain associated with dyspnea, weight loss, asthenia, adynamia, and hyporexia. An electrocardiogram showed signs of systolic left ventricular overload. An echocardiogram showed moderate mitral and tricuspid regurgitation, ejection fraction <15%, and bilateral pleural effusion. A rapid

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immunochromatographic screening test for IgG (Xerion) was conducted for Chagas disease and a serological test for hepatitis B. Both tests returned negative results. She presented neurological impairment due to sleepiness and a slow response to stimuli. Brain tomography showed a bifrontal hypodense left lesion and cerebral edema, and a diagnosis of encephalopathy was made. Consequently, treatment with sulfadoxine–pyrimethamine for a presumptive cerebral toxoplasmosis was implemented.

After 8 days of hospitalization, the patient did not show any improvement. Magnetic resonance imaging (MRI) showed a frontal lesion of left predominance, with peri-lesional edema causing a mass effect with a significant midline shift that was initially correlated with lymphoma. Considering that the patient reported persistent dyspnea, and given the evident extensive pleural effusion in the right hemithorax, a therapeutic thoracentesis was performed; only a lymphocyte-predominant exudate was observed in the pleural fluid. Thereafter, therapy with the broad-spectrum antibiotic meropenem, 1 g intravenously, was given every 8 h. Six days later, the patient's acute condition remained and her dyspnea had worsened. Antibiotic treatment was suspended. Afterwards, a decompressive thoracentesis and a lumbar puncture were performed, and flagellated parasites consistent with trypomastigotes were observed in both fluids (pleural and CSF). CSF analysis revealed normal cellularity, elevated protein (94.05 mg/dl), and low glucose (42.2 mg/dl). Rapid IgG serological tests with *T. cruzi* recombinant antigens (Wiener Laboratorios) were repeated over 3 days. Among the rapid serological tests, one negative result and two positive results were obtained. Accordingly, trypanocidal therapy with nifurtimox 8 mg/kg/day was administered over the course of 4 days following diagnosis. Unfortunately the patient died 1 day after therapy ceased.

Pathology, molecular detection, and characterization of *T. cruzi* analyses were conducted on post-mortem biopsies from the heart and brain tissues. Molecular detection using primers 121 and 122 targeted to the variable region of kinetoplast DNA was implemented. Moreover, molecular detection of the B1 gene of *Toxoplasma gondii* was performed using primers and PCR conditions reported previously, in order to rule out cerebral toxoplasmosis. Molecular characterization was conducted using the intergenic region of the mini-exon gene (SL-IR), the 24Sα and 18S regions of rDNA.[4] The results of the PCR conducted in both tissues were positive for *T. cruzi* kDNA, revealing a mixed infection in the heart by TcI and TcII (TcI/TcII), and only TcI in the brain. The amplification products of SL-IR, obtained from heart and brain tissues, were cloned and sequenced to discriminate TcI genotypes. A mixed infection by TcI sylvatic-type and TcI_{DOM} genotype was observed in the heart, while in the brain only TcI sylvatic-type was detected. To test the integrity of the DNA, we applied β-actin gene detection, which was positive. Pathology studies were conducted; myocarditis and pericarditis with a lymphocytic infiltrate in the heart and necrosis with lymphocytic infiltrate and numerous parasites in the brain were observed (Figure 1).

3. Discussion

Even considering the acute clinical manifestations, the case reported possibly represents a reactivation of Chagas disease due to co-infection with HIV/AIDS. The history of living in an endemic area is the main epidemiological criterion for suspecting *T. cruzi* infection.[5] The patient was born and had lived in the municipality of Cesar, where Chagas disease cases and the presence of triatomines such as *Rhodnius prolixus*, *Panstrongylus geniculatus*, *Eratyrus cuspidatus*, and *Belminus herreri*, have been reported previously. Consequently, she may have acquired the *T. cruzi* infection through the vector-borne route during childhood and the HIV infection later in life.

During hospitalization, the patient showed negative serology to Chagas disease and a necrotic lesion suggestive of neurotoxoplasmosis in the brain. The suspicion of neurotoxoplasmosis led to

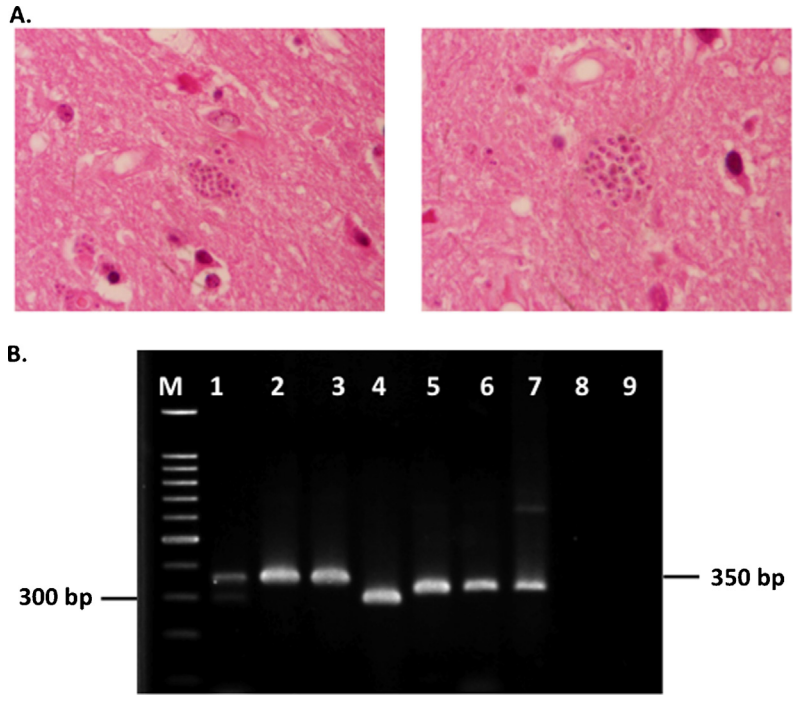

Figure 1. Detection and characterization of *Trypanosoma cruzi* in post-mortem biopsies from heart and brain tissues. (A) Hematoxylin and eosin stained sections from brain tissues; a *T. cruzi* amastigote nest is present in the brain tissue (original magnification ×100). (B) PCR amplification of DNA and characterization from *T. cruzi* present in tissues. Lanes 1–4 are amplification products of the intergenic region of the mini-exon: lane 1, heart tissue; lane 2, brain tissue; lane 3, TcI control (350 bp); lane 4, TcII control (300 bp). Lanes 5–7 are amplification products of kDNA: lane 5, heart tissue; lane 6, brain tissue; lane 7, TcI control (330 bp). Lanes 8 and 9 are negative controls. Electrophoresis on a 2% agarose gel visualized by staining with Gel Red 100-bp weight marker.

confusion in the diagnosis and inadequate administration of treatment. The alterations caused by *T. cruzi* in the brains of Chagas and HIV/AIDS co-infected patients show focal necrotic lesions indistinguishable from those caused by *T. gondii*. Consequently, these patients are frequently treated for cerebral toxoplasmosis, increasing mortality because of the delay in appropriate treatment.[2] In our case, *T. gondii* infection was excluded by a nested and sensitive PCR assay.

Worldwide, the major parasitic diseases considered as opportunistic infections for HIV/AIDS are toxoplasmosis, cryptosporidiosis, and cystoisosporiasis. In addition, several countries endemic for Chagas disease, including Brazil, Chile, and Argentina, have included *T. cruzi* on the list of opportunistic pathogens. However, in Colombia, despite reported cases, *T. cruzi* has not been included as an opportunistic pathogen in the protocols for the management of HIV/AIDS. It is noteworthy that timely specific therapy with benznidazole and nifurtimox has proven to be highly effective in cases of reactivation of Chagas disease, even if this treatment has not been formally incorporated into the management protocols for immunocompromised patients. It is even recommended that the specific therapy should be started before immunosuppression whenever possible to reduce the risk of reactivation.

We have described the molecular characterization of *T. cruzi* in a patient with HIV co-infection in Colombia. The findings highlight the usefulness of PCR as a complementary tool for the rapid, differential, and sensitive diagnosis of Chagas disease in HIV/AIDS patients. Lastly, the presence of mixed infection by TcI/TcII in the heart and TcI sylvatic-type in the brain, and the epidemiological data, suggest that the severity of symptoms should be attributed to co-infection by TcI genotypes associated with domestic and sylvatic cycles. These may show neurotropism and high pathogenicity in cardiac tissue resulting from a state of immunosuppression caused by HIV infection. This information is of paramount importance to understand the tissue tropism of *T. cruzi* DTUs and its possible relationship with the clinical manifestations of the disease.

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Conflict of interest: We declare no conflicts of interest.

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