

## CASE REPORT

# CHAGASIC MENINGOENCEPHALITIS IN AN HIV INFECTED PATIENT WITH MODERATE IMMUNOSUPPRESSION: PROLONGED SURVIVAL AND CHALLENGES IN THE HAART ERA

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### SUMMARY

The reactivation of Chagas disease in HIV infected patients presents high mortality and morbidity. We present the case of a female patient with confirmed Chagasic meningoencephalitis as AIDS-defining illness. Interestingly, her TCD4+ lymphocyte cell count was 318 cells/mm<sup>3</sup>. After two months of induction therapy, one year of maintenance with benznidazol, and early introduction of highly active antiretroviral therapy (HAART), the patient had good clinical, parasitological and radiological evolution. We used a qualitative polymerase chain reaction for the monitoring of *T. cruzi* parasitemia during and after the treatment. We emphasize the potential value of molecular techniques along with clinical and radiological parameters in the follow-up of patients with Chagas disease and HIV infection. Early introduction of HAART, prolonged induction and maintenance of antiparasitic therapy, and its discontinuation are feasible, in the current management of reactivation of Chagas disease.

**KEYWORDS:** Chagas disease; Meningoencephalitis; Central nervous system; Acquired immunodeficiency syndrome.

### INTRODUCTION

The co-infection *Trypanosoma cruzi*/HIV was first described in the 1990s, showing the opportunist character of *T. cruzi* in the presence of immunosuppression<sup>12,16,18</sup>. The Ministry of Health of Brazil included the reactivation of Chagas disease in the list of AIDS defining illness in 2004<sup>6</sup>. However, the true prevalence of co-infection is not well known, and its actual frequency of reactivation is estimated at 20%<sup>28</sup>. The magnitude of AIDS and Chagas disease in Brazil, as chronic conditions, increases the possibility of cases of reactivation therefore increasing the incidence of this medical condition<sup>3</sup>.

In Brazil there are about 2 to 3 million people infected with *T. cruzi*, where Chagas disease, as the underlying disease was the fourth leading cause of death (10.8%) among all infectious and parasitic diseases<sup>22</sup>. Furthermore, considering cases of HIV/AIDS, it was demonstrated that the frequency of co-infections was up to 1.3%<sup>19</sup>. A recent transversal study has reported a high rate of the disease reactivation in a co-infected population (41.2%), the central nervous system (CNS) being the main site of reactivation, representing 74% of cases. However, signs and symptoms are nonspecific, ranging from headache, intracranial hypertension, seizures, and coma leading to diagnostic confusion, mainly with toxoplasmosis and tumors of the central nervous system<sup>3</sup>.

Some of the predictors of the incidence of Chagas disease reactivation are the detection of parasitemia, low TCD4+ lymphocyte values (< 200 cells/mm<sup>3</sup>) and high viral load of HIV, although these are not essential to its occurrence<sup>3,9,12,23,27</sup>. Recently, it was suggested that the monitoring of reactivation must be performed by parasitemia and/or molecular analyses as well as the degree of immunosuppression<sup>15,17,27</sup>. The reactivation of Chagas disease in patients with HIV co-infection is associated with high mortality related to several factors, including the occurrence of reactivation in the CNS, which is frequently fatal without specific treatment<sup>2,3,29</sup>, and the severe immunosuppression of AIDS patients.

We report a case of meningoencephalitis caused by reactivation of Chagas disease in a patient with recent diagnosis of AIDS, who presented a favorable clinical, parasitological and radiological evolution after treatment with benznidazole and antiretroviral therapy.

### CASE REPORT

A forty-two-year-old female patient, who spent her childhood and adolescence in a rural area in Bahia State, has been living in an urban area of São Paulo State for the last 23 years. One month before admission, the patient was diagnosed with HIV infection. She was admitted to our hospital with a history of progressive loss of strength

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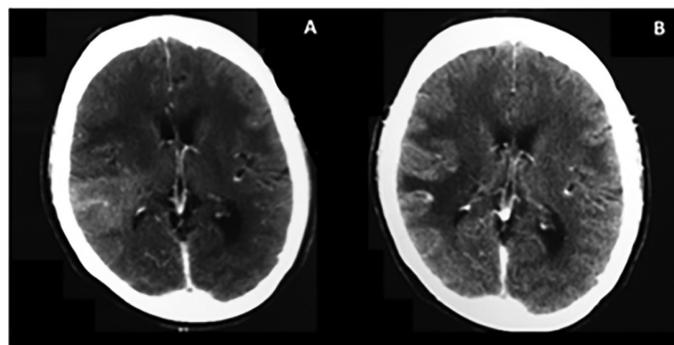
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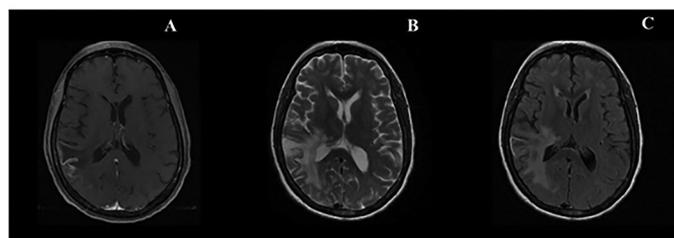
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in left upper and lower limbs, and seizures, for 15 days. On the day of admission, she presented a new seizure. Upon physical examination, the patient was febrile, hemodynamically stable, disoriented in time and space, and presenting left hemiparesis. Hemoglobin in blood revealed 15 mg/dL and leukocytes = 5000 cells/mm<sup>3</sup> (61% neutrophils, 29% lymphocytes, 8% monocytes). The biochemical tests did not detect any alterations. Cranial tomography (CT) scan showed findings compatible with encephalitis (Fig. 1A). Examination of cerebrospinal fluid (CSF) showed cells = 16 (94% lymphocytes, 6% monocytes, 0% neutrophils), proteins = 71 mg/dL, and glucose = 50 mg/dL. Blood and cerebrospinal fluid (CSF) cultures were performed to isolate bacteria, fungi and mycobacteria, and they showed no growth. Empirical treatment was initiated to cerebral toxoplasmosis with sulfadiazine, pyrimethamine and folinic acid combined with dexamethasone. The patient had TCD4+ lymphocyte count = 318 cells/mm<sup>3</sup> and HIV-1 RNA = 26.168 copies/mL. Serology for *Toxoplasma gondii* showed reactive IgG antibodies and non-reactive IgM antibodies. Ten days after the start of empirical treatment for cerebral toxoplasmosis, the patient presented nausea and vomiting associated with decreased level of consciousness. A new CT scan revealed increased mass effect in the right fronto-temporo-parietal area (Fig. 1B). Another lumbar puncture was performed showing cells = 5 (91% lymphocytes, 6% monocytes, 1% neutrophils), proteins = 42mg/dL, and glucose = 63mg/dL. The direct examination of CSF showed trypomastigotes compatible with *T. cruzi* and the polymerase chain reaction (PCR) identified DNA of this parasite<sup>19,30,33</sup>. PCR of the CSF for *T. gondii*; Epstein Barr virus and JC virus were negative. Serological tests for *T. cruzi* (ELISA and passive hemagglutination) were reactive with the latter presenting titration of 1:128. Heart and digestive involvement were excluded by echocardiogram, X-ray of the chest with barium contrast medium and barium enema, respectively. Direct analysis of *T. cruzi* in peripheral blood was negative, qualitative PCR was positive in blood, and blood culture was positive for *T. cruzi*. Benznidazole was prescribed, 5 mg/kg twice a day, and treatment for cerebral toxoplasmosis was interrupted. Two weeks later, the patient showed partial improvement of the focal deficit, still with limitations in walking and moderate psychomotor slowing. Zidovudine, lamivudine and lopinavir/ritonavir were introduced. Qualitative PCR monitoring of *T. cruzi* DNA in blood and CSF, on days seven, 14, 30, and 60 of treatment showed negative results. After two months of treatment with benznidazole, the patient showed clear neurological improvement, with residual hemiparesis, walking unaided, and with slight psychomotor slowing. At this time, magnetic resonance imaging (MRI) of the brain showed signs of meningoencephalitis in regression (Fig. 2). The patient was discharged with secondary prophylaxis, receiving benznidazole three times a week. Four months after diagnosis, the patient had progressive neurological improvement, with mild left hemiparesis and mild psychomotor slowing. A new MRI also showed improvement in the previously observed signs of disease (Fig. 3). Tests showed TCD4+ lymphocyte = 416 (18%) and HIV viral load < 50 copies/mL. After a year of follow-up, the patient remained with stable neurological sequelae (mild left hemiparesis and psychomotor slowing) and secondary prophylaxis with benznidazole was interrupted. Qualitative PCR in blood for *T. cruzi* was negative. The TCD4+ lymphocyte count was 349 (13%) and HIV viral load < 50 copies/mL. Six months after discontinuation of secondary prophylaxis, the patient remained clinically stable.

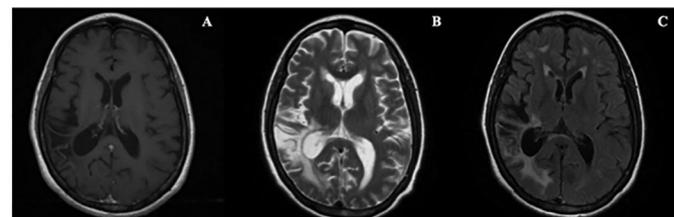
The parasite was identified directly in the blood by a three-marker sequential typing strategy<sup>19,30,33</sup> consisting of PCR amplification of the



**Fig. 1** - Contrasted brain computed tomography scan. A) CT at admission showing bilateral areas of gyral enhancement with regional edema, particularly in the right temporo-parietal region; B) CT after 10 days of admission showing persistent gyral enhancement and worsening of adjacent edema in the right temporo-parietal region.



**Fig. 2** - Magnetic resonance imaging two months after the diagnosis of chagasic meningoencephalitis. A) MRI T1 with gadolinium. Gyral enhancement in the right temporo-parietal region; B and C) MRI T2 and FLAIR, respectively. Focus of hyperintensity adjacent to the images described in T1.



**Fig. 3** - Magnetic resonance imaging four months after the diagnosis of chagasic meningoencephalitis. A, B and C) MRI T1 with gadolinium, T2 and FLAIR, respectively. Findings consistent with partial regression of the findings described two months before. The dilation of the posterior right lateral ventricle due to adjacent encephalomalacia is noted.

D7 divergent domain of the 24S $\alpha$  rDNA gene, PCR-RFLP of the heat shock protein 60 (HSP60) and glucose-6-phosphate isomerase as TC II, usually responsive to benznidazole.

## DISCUSSION

Although Brazil leads the number of cases of reactivation of Chagas disease in HIV-infected patients<sup>26</sup>, the real extension of the problem is unknown, due to underdiagnosis and underreporting of cases<sup>3</sup>. Vector-borne and transfusion transmission of Chagas disease have been successfully controlled in Brazil. Such measures are based on insecticide chemical treatment of dwellings in endemic areas and rigorous blood bank control<sup>14</sup>. Nevertheless, Chagas disease remains a public health concern in many geographic areas. The main scenario pertains to northeastern Brazil,

where the species *Triatoma brasiliensis* and *T. pseudomaculata* present potential epidemiological importance for transmission of disease in this area<sup>7,8</sup>. Both species have been captured in peridomestic environments and natural semiarid ecosystems, where high rates of *T. cruzi* infection have been reported<sup>30</sup>. Of note, our patient came from a rural area of Bahia and considering the eco-epidemiological situation, she probably acquired the infection through vectorial route.

Reactivation of Chagas disease in the CNS presents two frequent clinical forms: diffuse, acute or subacute meningoencephalitis (multiple foci of necrotic-encephalitis), and/or intracranial mass lesion, known as “chagoma” (isolated or multiple necrotic-hemorrhagic nodular lesions)<sup>26</sup>. At the *Instituto de Infectologia Emílio Ribas*, Sao Paulo, Brazil, in patients with meningeal syndrome, the most common causes are cryptococcosis, tuberculosis and syphilis. On the other hand, the syndromes in which there is a predominance of one or more brain mass lesions, are cerebral toxoplasmosis, tuberculomas, and CNS primary lymphoma<sup>21</sup>.

Considering the lack of specificity of clinical and radiological information, it is important to consider *T. cruzi* as a differential diagnosis in meningoencephalitis with or without focal brain lesion in patients with HIV/AIDS from countries where this disease is endemic and who lived in rural areas, are intravenous drug users, and also in those having received blood transfusion<sup>11,15,25</sup>. In chagasic meningoencephalitis, the diagnosis of reactivation is based on parasite visualization by direct microscopy in cerebrospinal fluid samples<sup>4,17</sup>. The diagnosis is often incidental, since more frequent etiologies are usually expected. Direct observation of the parasite in peripheral blood can help the diagnosis, however, it may be negative, as in the present case. The diagnosis of “chagoma” without meningoencephalitis is more difficult due to the need of pathological confirmation. The absence of anti-*Toxoplasma* antibodies in patients with HIV infection who have one or more expansive lesions should raise clinical suspicion of alternative diseases, including Chagas disease. The presence of anti-*T. cruzi* antibodies is important in the initial approach. On the other hand, patients without clinical and radiological improvement after 10-14 days of empirical treatment for cerebral toxoplasmosis should also be carefully reevaluated. Most patients with neurological reactivation of Chagas disease presents TCD4+ lymphocyte count < 200 cells/mm<sup>3</sup>. In a systematic review from 1980 to 2010, held in Brazil, 120 cases of reactivation of Chagas disease were evaluated and an average of TCD4+ lymphocytes of 98 cells/mm<sup>3</sup> was reported<sup>3</sup>. Most patients with neurological reactivation died shortly after diagnosis or during treatment<sup>29</sup>. The mortality rate is approximately 85%, even in patients receiving treatment, mainly due to delayed diagnosis and severe immunosuppression<sup>10</sup>. In contrast, in the present case, the patient presented low TCD4+ lymphocyte count but higher than 200 cells/mm<sup>3</sup>, a condition that may have modulated appropriately the therapeutic response even after neurological deterioration during the empirical treatment for cerebral toxoplasmosis with antiparasitic drug and corticosteroids. As previously described, higher rates of parasitemia appear to be related to higher doses of corticosteroids<sup>28</sup>. Nevertheless, in the present case, clinical manifestations of Chagas disease were present before the introduction of corticosteroids, suggesting that the major factor for reactivation was the immunosuppression related to AIDS.

There is scarce information on the clinical use of molecular techniques in HIV-infected patients with neurological manifestations in the context of reactivation of Chagas disease<sup>13,27</sup>. Qualitative positive

PCR in peripheral blood can be found in patients with chronic Chagas disease, making the diagnosis of reactivation even more difficult, being the gold standard represented by the identification of parasites by direct microscopy in biological fluids. On the other hand, qualitative or quantitative PCR are useful tools for therapeutic monitoring but little information is available in the CSF<sup>13,24</sup>. As noted in this case, we consider the sequential results of qualitative PCR in both peripheral blood and cerebrospinal fluid for therapeutic monitoring, always in combination with clinical and radiographic findings. Opportune treatment with benznidazole may help to improve survival rates. Nevertheless, long-term prognosis of HIV-infected patients who have neurological reactivation of Chagas disease depends on the immunological and virological control due to the use of antiretroviral therapy<sup>15,21</sup>.

Before the advent of HAART, the prognosis of Chagas disease reactivation in HIV-infected patients was poor<sup>15</sup>. Based on cases reported in the literature after the HAART era, survival reaches three to five years. In all of these cases and as shown in our patient, therapy for Chagas disease was maintained for a long period and secondary prophylaxis was continued until virological suppression and substantial immune recovery were achieved<sup>11,15</sup>. Moreover, the discontinuation of secondary prophylaxis is an issue still unknown but usually performed as an extrapolation of the management of other opportunistic infections<sup>15</sup>. Considering that there are no well documented cases of inflammatory syndrome of immune reconstitution associated with Chagas disease, the current recommendation is to start or adjust antiretroviral therapy as soon as the patient is clinically stable<sup>24</sup>. In the present case, HAART was initiated two weeks after the initiation of the antiparasitic treatment. The duration of Chagas disease treatment has not been formally evaluated in HIV-infected patients, but benznidazole is recommended, 5-8 mg/kg/day, orally, in two doses for 60 days. The need, composition, and duration of the maintenance treatment are also controversial, particularly in the HAART era. However, considering the available information, we prescribed benznidazole 2.5-5 mg/kg/day, three times a week, until stable immune reconstitution was achieved<sup>5,11,32</sup>. In the presence of reactivation with 318 TCD4+ lymphocytes count, we suggest that the effective control of viremia by HAART associated with a period of maintenance treatment of six-12 months, increased TCD4+ lymphocyte count, and negative PCR in blood may represent sufficient parameters for discontinuation of the antiparasitic therapy.

In conclusion, we report the case of a patient with chagasic meningoencephalitis as AIDS-defining illness, despite having TCD4+ lymphocyte counts > 200 cells/mm<sup>3</sup>. We emphasize the potential value of therapeutic monitoring using molecular techniques, associated with clinical and radiological parameters. Nowadays, early introduction of HAART, prolonged induction and maintenance of antiparasitic therapy, and its discontinuation represent real targets in the current management of reactivation of Chagas disease in HIV-infected patients.

## RESUMO

### **Meningoencefalite chagásica em paciente infectada pelo HIV com imunodepressão moderada: desafios na era HAART e sobrevida prolongada**

A reativação da doença de Chagas em pacientes com a infecção pelo HIV apresenta uma alta morbidade e mortalidade. Neste relato,

apresentamos caso confirmado de meningoencefalite chagásica, como doença definidora de aids, em paciente com 318 linfócitos T-CD4+/mm<sup>3</sup>. Após 2 meses de tratamento seguido de um ano de profilaxia secundária com benzonidazol e início precoce de terapia antirretroviral (HAART), a paciente apresentou boa evolução clínica, parasitológica e radiológica. Utilizamos a reação em cadeia da polimerase qualitativa do *T. cruzi*, para monitorização da parasitemia por *T. cruzi* durante e após o tratamento. Ressaltamos o valor potencial das técnicas moleculares associadas aos parâmetros clínicos e radiológicos nos pacientes com doença de Chagas e infecção pelo HIV. A introdução precoce da terapia antirretroviral, a terapia antiparasitária prolongada, manutenção e descontinuação da mesma, são desafios atuais, embora possíveis, no manejo da reativação da doença de Chagas na era das terapias antirretrovirais de alta eficácia.

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### POTENTIAL CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest

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