Reactivation of Chagas’ Disease in Patients with AIDS: Report of Three New Cases and Review of the Literature

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Three new cases of reactivation of Chagas’ disease in patients with AIDS, with central nervous system and/or cardiac involvement, are reported. One patient had histological evidence of acute esophageal and gastric Trypanosoma cruzi myositis, a previously unrecognized finding in patients with reactivated Chagas’ disease. The patients had a low CD4 lymphocyte count and had other AIDS-defining opportunistic infections. One patient’s condition improved with benznidazole therapy. Analysis of these three cases and review of the 13 others published in the literature revealed that the central nervous system is the most commonly involved site (75%), followed by the heart (44%). Early diagnosis and treatment with benznidazole or nifurtimox probably improve the survival rate. Long-term secondary prophylaxis should be recommended for patients who respond to therapy, although it is uncertain which drug to use for this purpose. T. cruzi should be included in the list of opportunistic pathogens causing infection in severely immunocompromised patients with AIDS.

Chagas’ disease is one of the most important parasitic diseases in Latin America. The infection, caused by the protozoon Trypanosoma cruzi, is transmitted mainly by vectors (reduviid bugs) or by blood transfusion. It is estimated that between 16 and 18 million people are chronically infected with T. cruzi, in the Americas and that >90 million people are at risk of acquiring this infection [1]. The acute phase of the disease can be oligosymptomatic and nonspecific and therefore not clinically recognized. The majority of chronically infected individuals are also asymptomatic (indeterminant form of the disease), but in the long run ~25% develop clinically recognized cardiac disease and 1% develop megaesophagus or megacolon [2].

Reactivation of the disease in individuals with chronic Chagas’ disease, manifested as a febrile syndrome accompanied by meningoencephalitis and/or myocarditis, has been associated with immunodeficiency states such as those caused by hematologic malignancies, kidney and heart transplantation, and corticosteroid therapy [3–5]. Recently, reactivation of Chagas’ disease has also been observed in patients with HIV infection, sometimes as the first opportunistic infection [6–19]. The case-fatality rate among patients with AIDS reported so far has been extremely high, even when the diagnosis was made and appropriate therapy was instituted.

We report three new cases of reactivation of Chagas’ disease in patients with AIDS, review the cases reported in the literature so far, and comment on the need for early diagnosis, treatment, and prophylaxis for this protozoon infection, aiming at decreasing the case-fatality rate among these immunocompromised individuals.

Case Reports

Case 1. A 27-year-old bisexual drug-addicted male was admitted to the hospital because of high fever, chills, weight loss, coughing, and vomiting that had started 4 weeks before. For 4 years it had been known that he was infected with HIV and had chronic Chagas’ disease in its indeterminate phase, the latter confirmed by indirect immunofluorescence (IF), ELISA, and passive hemagglutination (PH) tests. The only previous opportunistic infection was an episode of oral thrush 2 years before. He was not receiving antiretroviral agents, which were unavailable from the Brazilian Ministry of Health at the time. Positive physical examination findings included a temperature of 39°C, tachycardia, dehydration, cervical adenopathy, hepatomegaly, and rales in the right hemithorax.

A blood count revealed anemia, leukopenia (2,700 leukocytes/mL), and lymphopenia (810 lymphocytes/mL); 6 months before, he had had 102 CD4 lymphocytes/mL. The CSF was normal; direct examination was negative for T. cruzi, fungi, and acid-fast bacilli.

Radiologic examination of the chest revealed consolidation of the right lower lung and right pleural effusion. A pleural biopsy was performed, and Rhodococcus equi grew in a culture of a fragment of pleural tissue. An electrocardiogram revealed sinus tachycardia, incomplete right-bundle-branch block, enlargement of the QTC, and QRS complexes of low amplitude. Echocardiographic findings were enlargement of the left chambers and pericardial effusion. It is uncertain whether the electrocardiographic and echocardiographic findings were related to reactivation of the trypanosomiasis in the heart or were manifestations of chronic cardiac involvement that had appeared during the preceding 4 years.
CT scanning of the brain showed four hypodense lesions with weak enhancement by contrast. Direct examination of thick blood smears repeatedly revealed *T. cruzi*. A serological test (ELISA) for toxoplasmosis was negative for IgM and IgG antibodies.

This patient received treatment with benznidazole (8 mg/[kg·d]) for 50 days, during which the direct examination for *T. cruzi* in thick blood smears became negative, and a control CT scan after 30 days of treatment was normal. Since no drugs were given concurrently with benznidazole, the improvement observed on the CT scan is evidence that this drug was effective. Benznidazole administration was interrupted because of the appearance of severe peripheral neuropathy. Pleuropulmonary infection by *R. equi* was treated with vancomycin plus erythromycin. During follow-up the patient developed severe (possibly benznidazole-related) neutropenia and died of sepsis. A postmortem examination was not performed.

**Case 2.** A 48-year-old bisexual man with severe headache, fever, cough, dyspnea, and left hemiparesis was admitted to the hospital. CSF examination revealed 69 leukocytes/mL, 96% of which were neutrophils; the protein value was 158 mg/dL, and the glucose level was 12 mg/dL. A chest radiograph showed heterogeneous consolidation of the right middle lobe. A CT scan of the brain showed no abnormalities. Serological tests for Chagas’ disease (IF and ELISA), HIV infection (ELISA), and hepatitis B surface antigen (ELISA) were positive. The CD4 lymphocyte count was 264/mL. Thick blood smears from two different samples were positive for *T. cruzi*.

The patient was given broad-spectrum antibiotics, benznidazole (5 mg/[kg·d]), and amphotericin B, and died 72 hours later. Postmortem examination revealed pulmonary cryptococcosis and cytomegalovirus infection, chronic active hepatitis, and nonspecific focal myocarditis. The brain was not examined, and it is therefore uncertain whether the meningoencephalitic involvement was due to *T. cruzi*. The parasite was not found in any organ, even with the use of immunohistochemical techniques.

**Case 3.** A 39-year-old heterosexual female, known to have Chagas’ disease (by ELISA, IF, and PH test) in its chronic indeterminate form, as well as HIV infection of at least 5 years’ duration, was admitted to the hospital with congestive heart failure, weight loss, and pallor. She had received didanosine for 1 year and had a history of herpes zoster, neurotoxoplasmosis, and oral and esophageal candidiasis, all successfully treated with standard therapies. Laboratory tests revealed severe anemia (hemoglobin, 5 g/dL) and a CD4 lymphocyte count of 136/mL. Chest radiography revealed cardiomegaly and bilateral pulmonary interstitial infiltrates. Pericardial effusion was detected by an echocardiogram. A brain CT scan was normal. Direct examinations for *T. cruzi* in the blood and CSF were negative.

The patient died in 2 days of acute respiratory failure. Postmortem examination revealed evidence of acute and chronic myocarditis, with countless *T. cruzi* amastigote nests, and gross pericardial effusion. Trypomastigote forms of *T. cruzi* were seen on direct examination of the pericardial fluid. Acute *T. cruzi* myositis of the esophagus and stomach, cryptococcosis of the spleen, disseminated mycobacteriosis, adrenal cytomegalovirus infection, and esophageal candidiasis were also observed. Immunohistochemical studies confirmed the identity of *T. cruzi* in the myocardium, esophagus, and stomach.

**Literature Review and Discussion**

In Brazil, transmission of Chagas’ disease by the reduviid bug, as well as by transfusion of blood and blood products, has been controlled in the past decade. Because of migration from rural areas, chronic Chagas’ disease has become mostly an urban disease, and it is estimated that currently ~60% of the 5 million Brazilian case-patients are living in cities [20]. Chagas’ disease is also an urban disease in other Latin American countries and in the United States [5, 21]. The majority of the cases of HIV infection in these countries are also found in urban areas, and therefore it is expected that coinfections occur.

Since the recognition of AIDS, the theoretical possibility of the appearance of cases of reactivated Chagas’ disease among patients with coinfections with HIV and *T. cruzi* has been discussed. Gluckstein et al. [10] recognized the first case, although its publication was preceded by cases reported by Del Castillo et al. [6] and Ferreira et al. [8]. By November 1996, 13 cases had been published in the literature, although we are aware of at least 37 others that have been reported only in medical congresses [16]. In table 1, relevant data about the published cases and the ones reported herein are summarized.

The CNS was the most commonly involved site (12 of 16; 75%). The usual manifestations were acute meningoencephalitis, unifocal or multifocal, with fever, headache, vomiting, seizures, and focal neurological signs. Analysis of the CSF showed mild pleocytosis (<100 cells/mL), predominantly of lymphocytes, an increased protein level, and the presence of *T. cruzi* trypomastigotes. These findings are consistent with those of acute Chagas’ disease and of reactivated Chagas’ disease in other immunocompromised individuals [4, 22]. The parasites usually were also seen in the blood by direct examination, such as in our case 1.

CT scanning of the brain revealed single or multiple hypodense lesions, with or without ring enhancement, predominantly in subcortical areas, a finding that can be useful for differential diagnosis with toxoplasmosis, in which involvement of the thalamus and basal ganglia is more common [23]. The lesions were found in the brain lobes, cerebellum, and brain stem and predominantly involved the white matter [16]. Histologically, a severe inflammatory infiltrate was observed, with countless amastigote forms of *T. cruzi* parasitizing glial cells and, rarely, neurons [16]. Parasites were found within macrophages in the meninges. Confirmation of the identity of the parasite by immunohistochemical methods or electron
Table 1. Data from cases of AIDS and reactivation of Chagas’ disease.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>[reference]</th>
<th>Patient’s age (y)/sex</th>
<th>ME-E/encephalitis</th>
<th>CD4 lymphocytes (mL)</th>
<th>Serological test result</th>
<th>Blood</th>
<th>CSF</th>
<th>Treatment</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>[6]</td>
<td>19/M</td>
<td>Y/Y*</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
<td>NR</td>
<td>Surg/Nif</td>
<td>&gt;3 mo</td>
</tr>
<tr>
<td>2</td>
<td>[8]</td>
<td>37/M</td>
<td>Y/N</td>
<td>NR</td>
<td>+</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>[9]</td>
<td>26/F</td>
<td>NR</td>
<td>45</td>
<td>+</td>
<td>X</td>
<td>NR</td>
<td>Bzn</td>
<td>2 mo</td>
</tr>
<tr>
<td>4</td>
<td>[10]</td>
<td>32/M</td>
<td>Y/N</td>
<td>35</td>
<td>+</td>
<td>NR</td>
<td>Y</td>
<td>Bzn/Itra/Flu</td>
<td>&gt;6 mo</td>
</tr>
<tr>
<td>5</td>
<td>[13, 19]</td>
<td>31/M</td>
<td>Y/N</td>
<td>NR</td>
<td>+</td>
<td>X</td>
<td>NR</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>[13]</td>
<td>40/M</td>
<td>N/Y</td>
<td>NR</td>
<td>+</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>[17]</td>
<td>40/M</td>
<td>N/Y</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>[7]</td>
<td>33/M</td>
<td>Y/N</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Y</td>
<td>Nif</td>
<td>2 mo</td>
</tr>
<tr>
<td>9</td>
<td>[15]</td>
<td>52/M</td>
<td>Y/Y</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>[12]</td>
<td>33/M</td>
<td>Y/Y</td>
<td>382</td>
<td>+</td>
<td>Y</td>
<td>Y</td>
<td>Bzn</td>
<td>3 mo</td>
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<tr>
<td>12</td>
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<td>104</td>
<td>+</td>
<td>Y</td>
<td>N</td>
<td>Bzn</td>
<td>20 d</td>
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<td>+</td>
<td>N</td>
<td>Y</td>
<td>Bzn</td>
<td>2 d</td>
</tr>
<tr>
<td>14</td>
<td>[PR, case 1]</td>
<td>27/M</td>
<td>Y/Y*</td>
<td>102</td>
<td>+</td>
<td>Y</td>
<td>N</td>
<td>Bzn</td>
<td>2 mo</td>
</tr>
<tr>
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<td>[PR, case 2]</td>
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<td>Y/N*</td>
<td>264</td>
<td>+</td>
<td>Y</td>
<td>N</td>
<td>Bzn</td>
<td>3 d</td>
</tr>
<tr>
<td>16</td>
<td>[PR, case 3]</td>
<td>39/F</td>
<td>N/Y*</td>
<td>136</td>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

NOTE. Bzn = benznidazole; Flu = fluconazole; Itra = itraconazole; ME-E = meningoencephalitis/encephalitis; N = no; Nif = nifurtimox; NR = not reported; PR = present report; Surg = surgery; X = xenodiagnosis; Y = yes.
* Not confirmed.
² T. cruzi present in pericardial fluid.

microscopy is desirable in order to allow differential diagnosis with other parasites, particularly *Toxoplasma gondii*.

The heart was the second organ in frequency to be involved in the reactivation of Chagas’ disease (recognized in seven cases [44%], two of them not confirmed by isolation of the parasite in the tissue), but not all of the patients were systematically examined for cardiac involvement. The clinical manifestations were those of acute heart failure or arrhythmias, although some patients were asymptomatic. One of our patients (case 3) had two unusual manifestations of Chagas’ disease reactivation: presence of the parasite in the pericardial fluid, which was reported only once before in a patient with hematologic malignancy [4], and evidence of acute involvement of the esophagus and stomach, a previously unrecognized finding in patients with HIV infection although already noted in two patients with lymphoma [24, 25]. We identified another patient (case 2), who was probably in an early phase of reactivation and for whom the only evidence of Chagas’ disease reactivation was the finding of *T. cruzi* in the blood on direct examination.

The seven patients whose CD4 lymphocyte counts were determined had low counts, ranging from 35/mL to 382/mL. The majority of the patients simultaneously had several opportunistic infections, although not always recognized antemortem, suggesting that Chagas’ disease reactivation occurs when the cellular immunity is already compromised.

Early diagnosis of Chagas’ disease reactivation in HIV-infected patients can be made by the direct examination of blood or CSF of individuals likely to be chronically infected with the parasite, i.e., those coming from areas of endemicity in Latin American countries [1]. Trypomastigote forms of *T. cruzi* can be seen in smears of body fluids prepared with Giemsa stain; alternatively, direct examination of fresh, unstained preparations can reveal the motile parasites. Repeated examinations are sometimes necessary to increase the sensitivity of the test; a single negative direct examination does not exclude the diagnosis and is probably the reason why the parasite was not found in our case 3.

Although it has not been attempted for patients with HIV infection, *T. cruzi* can probably be isolated from blood cultured in special media (NNN or Schneider) [26], because of the large number of circulating parasites. Positivity of a blood culture or of a xenodiagnostic test should not be interpreted as evidence of reactivation, since a test is positive for the majority of patients with chronic Chagas’ disease [26, 27].

Early treatment is probably very important to improve the prognosis, as demonstrated in case 1. So far the survival time has been very short and the case-fatality rate has been very high, which are more likely to be due to delays in diagnosis than to inadequate therapy. The median duration of survival in the reported cases was 10 days, and only three patients survived as long as or longer than 3 months.

Benznidazole and nifurtimox are both effective for the treatment of reactivated Chagas’ disease in immunocompromised patients [28]. Benznidazole is presently given in a recommended daily oral dosage of 5 mg/kg (divided into two doses), and nifurtimox is also given by the oral route, as 8–10 mg/kg in three doses; both drugs should be administered for at least 60 days. Possible side effects of benznidazole are dermatitis,
peripheral neuropathy, and, more rarely, granulocytopenia, which can be of late onset (after >30 days of treatment) [29].

Administration of benznidazole had to be interrupted in our case 1 owing to severe peripheral neuropathy, and the same patient developed neutropenia, which was possibly related to the drug, although we cannot rule out the possible role of vancomycin in its origin [30]. Nifurtimox causes side effects, which include gastric intolerance, weight loss, peripheral neuropathy, psoriasis, dermatitis, and leukopenia [29].

Remission of the disease should be documented by the negativity of the direct examination, blood culture, and xenodiagnosis [31]. Among the five patients with reactivated Chagas’ disease who were treated and survived for at least 2 months, postmortem examination was performed on one (who died from septicaemia) and no parasites were found, suggesting the effectiveness of the therapy [12].

Secondary prophylaxis for patients with AIDS should be indicated on theoretical grounds (there has been no experience with acute myocarditis and reactivated Chagas’ disease in a patient with Trypanosoma cruzi). Whether primary prophylaxis is indicated remains to be determined. Secondary prophylaxis for patients with AIDS should be indicated on theoretical grounds (there has been no experience with acute myocarditis and reactivated Chagas’ disease in a patient with Trypanosoma cruzi). Nevertheless, a committee of experts has recently recommended that benznidazole, in a single oral dose of 5 mg/kg 3 times a week for life, should be the drug of choice, the alternative being oral nifurtimox at a dosage of 5 mg/kg 3 times a week [32]. Allopurinol or triazole derivatives are other theoretical possibilities, perhaps more suitable for chronic use [19, 33]. Whether primary prophylaxis would benefit HIV-infected individuals with chronic Chagas’ disease is also unknown.

References