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Reactivation of Tumor-like Chagas Disease in the Central Nervous System in Cardiac Transplant Patients: A Case Series and Literature Review

Reativação pseudotumoral da doença de Chagas no sistema nervoso central em pacientes transplantados cardíacos: Série de casos e revisão de literatura

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Abstract

Introduction Chagas disease is an important public health problem in Latin American countries, affecting ~ 6 million people within the region. In patients with chronic Chagas disease who undergo some type of immunosuppression reactivation of the acute form may occur, and manifestations involve many organs, including the central nervous system. Tumor-like brain reactivations are well described in patients with acquired immunodeficiency syndrome; however, this is a very rare event among Chagasic patients immunosuppressed after a heart transplantation.

Case Report We describe three cases of cardiac transplant patients who had a tumor-like intracranial lesion, whose biopsies were compatible with Chagas disease. All 3 patients were treated with benznidazole, and 2 of them presented parameters of cure after 60 days of treatment, while 1 required a 2nd cycle of treatment.

Discussion A tumor-like Chagas disease reactivation in the central nervous system may happen in heart-transplant patients and, due to the multiple differential diagnoses, we believe that brain biopsies should be considered when feasible.

Keywords
- Chagas disease
- central nervous system diseases
- heart transplantation
- immunosuppression therapy

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Resumo

Introdução A doença de Chagas é um problema de saúde pública relevante nos países da América Latina, afetando aproximadamente 6 milhões de pessoas na região. Em pacientes com a forma crônica da doença submetidos a algum tipo de imunossupressão, a reativação da forma aguda pode ocorrer e cursar com manifestações que envolvem vários órgãos, incluindo o sistema nervoso central. A reativação cerebral pseudotumoral é bem descrita em pacientes imunossuprimidos pela síndrome de imunodeficiência adquirida; contudo, é um evento raro entre os pacientes imunossuprimidos após transplante cardíaco.

Relato de caso São relatados três casos de transplantados cardíacos que apresentavam uma lesão tumoral intracraniana, cujas biópsias eram compatíveis com a doença de Chagas. Todos os 3 pacientes foram tratados com benznidazol, e 2 deles apresentaram parâmetros de cura após 60 dias de tratamento, enquanto 1 exigiu um 2° ciclo de tratamento.

Discussão A reativação pseudotumoral da doença de Chagas no sistema nervoso central pode acontecer em pacientes submetidos ao transplante cardíaco e, devido aos múltiplos diagnósticos diferenciais, acreditamos que a biópsia cerebral deve ser considerada quando viável.

Palavras-chave

- doença de Chagas
- doenças do sistema nervoso central
- transplante de coração
- imunossupressão

Introduction

Chagas disease (CD) or American trypanosomiasis is a zoonosis caused by the protozoan *Trypanosoma cruzi*. It is an important public health problem in Latin American countries, affecting ~ 6 million people within the region.[1] This disease presents an acute phase that is usually asymptomatic or oligosymptomatic and, in the absence of specific treatment, lasts 8 to 12 weeks. Once the host's immune response is able to reduce the replication of the parasite, the patient enters the chronic phase, which persists for his entire life. The chronic form of the disease comprises an asymptomatic latency period that can last for several years. The symptomatic chronic manifestation occurs in ~ 20 to 30% of those infected, with heart and gastrointestinal disease being its most common forms.[2]

The heart is the most affected organ in the chronic symptomatic phase of CD.[3] In patients with the chronic form and some type of immunosuppression, reactivation of the acute form may occur with manifestations involving various organs, such as the heart, skin, and the central nervous system. In advanced cases of Chagasic cardiomyopathy, heart transplantation is the chosen procedure, and these patients are at risk of reactivation as a result of the immunosuppressant therapy.

Three cases of patients who have undergone heart transplantation due to Chagasic cardiomyopathy and evolved with neurological symptoms are described. They underwent brain biopsy, and the result was compatible with cerebral CD. Furthermore, a literature review was performed through the PUBMED database searching for articles in English, Portuguese, and Spanish, with no date limit. The descriptors used were: *Chagas disease*, *American trypanosomiasis*, *central nervous system*, *cardiac transplant* and *immunosuppression*.

Case Reports

Case 1

A 47-year-old male patient was admitted to the emergency room after his first generalized tonic-clonic seizure. He was alert, oriented, afebrile, without focal neurological deficits and without neck stiffness. The patient had undergone a heart transplant 7 months prior to admission due to Chagasic cardiomyopathy. He reported daily headache that started after the transplant, with a worsening in intensity in the last 3 days, associated with apathy and behavioral changes. In addition, he had chronic renal failure and cataracts. The patient was taking the following medications: cyclosporine 200 mg/day, mycophenolate mofetil 2 g /day, tacrolimus 4 mg/day, prednisone 10 mg/day, diltiazem 10 mg/day, simvastatin 20 mg/day, metformin 500 mg/day, alendronate 70 mg/week, calcium carbonate 1,000 mg/day, and sulfamethoxazole-trimethoprim 400/80 mg/day.

The computed tomography (CT) scan without contrast showed left frontal hypodensity associated with perilesional edema. The magnetic resonance imaging (MRI) showed an expansive left frontal lesion with hyposignal in T1, heterogeneous enhancement by gadolinium, perilesional edema, and absence of restriction to diffusion (►**Fig. 1**). The patient underwent a lumbar puncture that showed an opening pressure of 23 cmH2O, and the other results of biochemistry, cytology, and microbiology were normal. Serological tests for toxoplasmosis and human immunodeficiency virus (HIV) tests were negative.

Due to the atypical lesion in an immunosuppressed patient with a history of CD, a brain open biopsy was chosen. Concomitantly, empirical treatment with benznidazole 300 mg/day was started. Histology showed neutrophilic and histiocytic inflammatory infiltrate, mainly perivascular, associated with amastigotes nests, compatible with CD

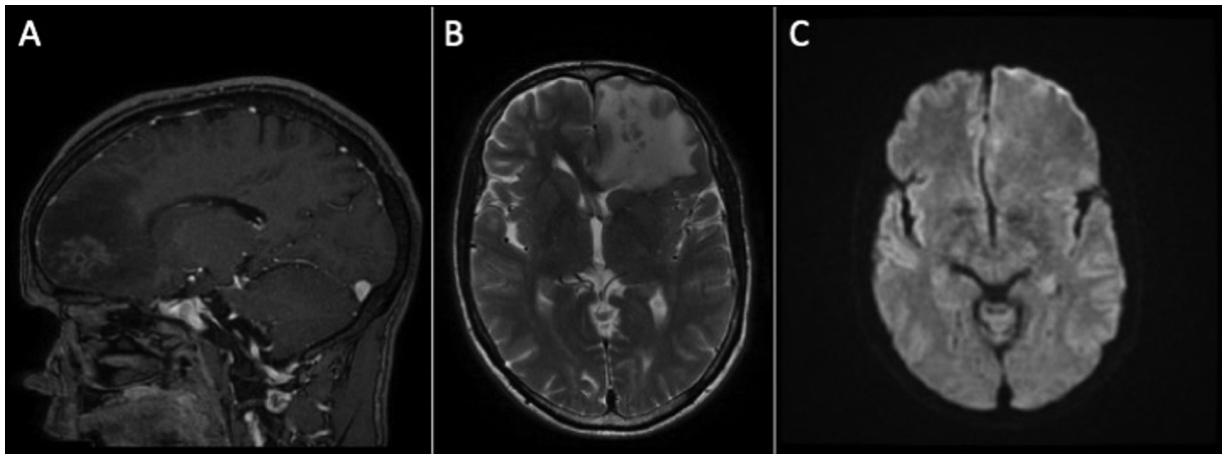

Fig. 1 Brain magnetic resonance imaging (MRI) of the case 1. (A) T1-weighted MRI with gadolinium. Note the heterogeneous contrast enhancement. (B) T2-weighted MRI shows heterogeneous lesion with intense perilesional edema. (C) Diffusion-weighted imaging MRI showing absence of restriction on diffusion.

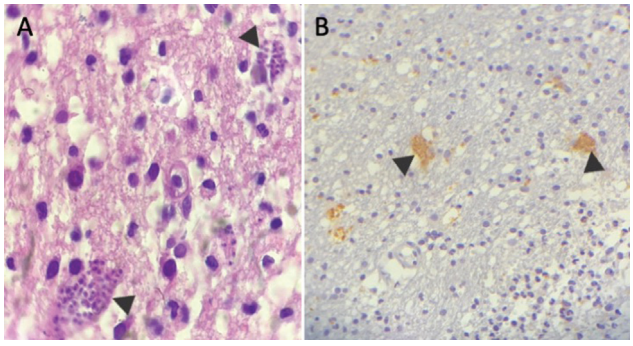

Fig. 2 (A) Hematoxylin-eosin stain with inflammatory infiltrate and amastigotes nests (arrows). (B) Immunohistochemistry analysis positive for the presence of *T. cruzi* (arrows).

(►**Fig. 2A**). Immunohistochemistry confirmed the diagnosis (►**Fig. 2B**). The patient was treated with benznidazole for 60 days and showed complete improvement. He had no new neurological symptoms after 3 years of follow-up.

Case 2

A 48-year-old female patient was admitted to the emergency department with left fasciobraquiocrural hemiparesis and dysarthria initiated in the last hours. There was a report of progressive headache of about 4 months of evolution and chronic hepatitis B being treated with entecavir. She underwent a heart transplant 4 months before admission as a result of Chagasic cardiomyopathy. The immunosuppression regimen was performed with cyclosporine 200 mg/day, prednisone 10 mg/day, and mycophenolate mofetil 2 g/day.

Image propaedeutic showed an extensive lesion in the right temporo-parietal region with the predominantly annular enhancement by gadolinium (►**Fig. 3**). Serological tests for toxoplasmosis and HIV tests were negative. We opted for an open biopsy of the lesion. In the hematoxylin-eosin stain, numerous parasites were observed forming amastigotes nests (►**Fig. 4**). Immunohistochemistry confirmed the diagnosis of reactivation of CD. After diagnosis, treatment with

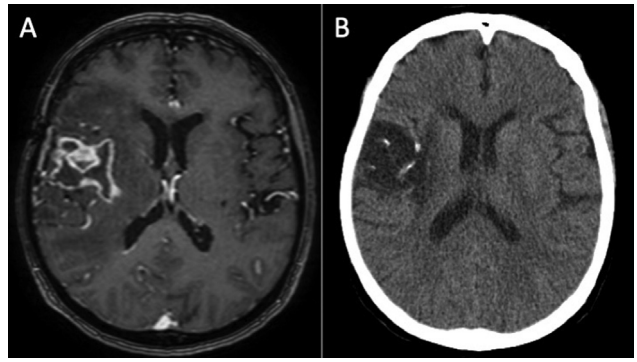

Fig. 3 (A) Magnetic resonance imaging of the brain in axial section in T1-weighted sequence with the presence of an expansive lesion with hyposignal and predominantly annular enhancement by gadolinium. (B) Computed tomography of the skull in axial section at the same level. Note non-specific hypodensity associated with intralesional bleeding.

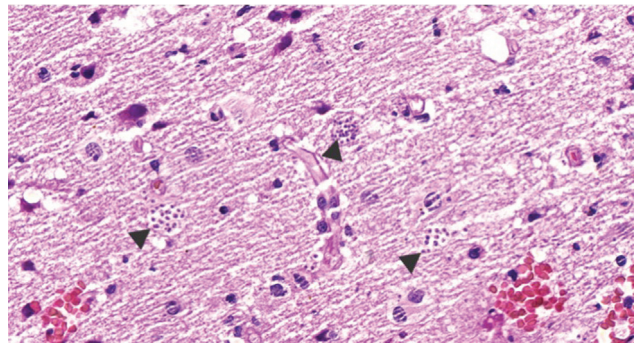

Fig. 4 Hematoxylin-eosin stain showing several nests of amastigotes (arrows) associated with inflammatory infiltrate.

benznidazole was started. After completing 60 days of treatment and partial improvement, the patient presented a further worsening of the deficit. Magnetic resonance imaging examination showed worsening of the lesions. The patient underwent a new benznidazole cycle with improvement of the condition but maintained a sequel motor deficit and dependence for basic activities.

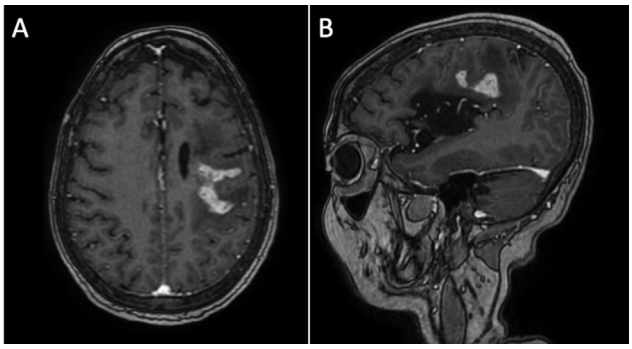

Fig. 5 Magnetic resonance imaging of brain in axial (A) and sagittal (B) section in T1-weighted sequence with presence of expansive lesion with hyposignal and heterogeneous enhancement by gadolinium.

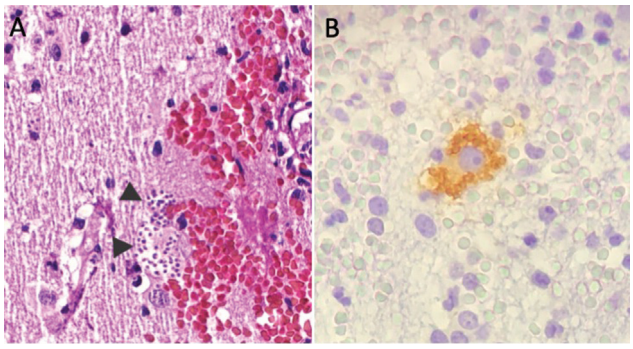

Fig. 6 (A) Hematoxylin-eosin stain with intracellular amastigotes (arrows) adjacent to an area of hemorrhagic necrosis. (B) Positive immunohistochemistry for *T. cruzi*.

Case 3

A female patient, 67 years-old, presented with a sudden onset of aphasia. She had undergone a heart transplant 4 months before admission due to Chagasic cardiomyopathy and used prednisone 5 mg/day, cyclosporine 150 mg/day, mycophenolate mofetil 1 g/day, and prophylaxis for neurotoxoplasmosis with trimethoprim sulfamethoxazole. Propaedeutics demonstrated a heterogeneous right frontal-temporal lesion with enhancement by paramagnetic contrast (►**Fig. 5**). Cerebrospinal fluid was not positive for research of *T. cruzi*, and biochemistry as well as cytology were normal. Serological tests for toxoplasmosis and HIV tests were negative. Cerebral open biopsy showed necrotizing encephalitis with the presence of amastigotes, and immunohistochemistry was positive for CD (►**Fig. 6**). The patient underwent treatment with benznidazole and maintained motor aphasia after 6 months of follow-up.

Discussion

In Latin America, Chagasic cardiomyopathy is the third most common cause of indication for heart transplantation.[4] Posttransplant immunosuppressive therapy increases the risk of *T. cruzi* infection reactivation, whose incidence after transplantation varies from 8 to 90%. This event is defined as an increase in parasitemia that can be detected by direct parasitological techniques or polymerase chain reaction (PCR), even in the absence of symptoms.[1,5,6]

Reactivation of CD is associated with immunodeficiency states, such as those caused by the acquired immunodeficiency syndrome (AIDS), hematological neoplasms, corticosteroid therapy, and other immunosuppressants, including in the context of solid organ transplantation.[7] General clinical manifestations observed include fever, myocarditis, symptoms suggestive of rejection or dermatological manifestations, including inflammatory panniculitis and skin nodules.[4] When the central nervous system is involved, the most common manifestations include headache, vomiting, seizures, and focal neurological deficits. The involvement of the central nervous system in reactivation is well described for patients with AIDS, accounting for up to 80% of cases.[8] In these patients, the most common form of presentation is meningoencephalitis, which may also present itself as tumor-like expansive lesions similar to abscesses, described by some authors as cerebral chagoma.[7,8] Cerebral chagoma is characterized by the presence of single or multiple nodular lesions with necrotic-hemorrhagic tissue, which are little and defined, but can evolve and reach bigger dimensions. These lesions are usually located in the white matter of the brain lobes, but they also affect the brainstem. Histologically, there is inflammatory infiltrate in the nervous and perivascular tissue, in addition to abundant intracellular amastigotes.[8] Magnetic resonance imaging reveals an expansive lesion with mass effect with T1 hyposignal, T2 hypersignal, and irregular or annular gadolinium enhancement, as shown in the cases described.

The first report of the brain tumor-like form reactivation of CD was made in 1973, by Queiroz,[6] in a patient with cutaneous T-cell lymphoma (mycosis fungoides). Since then, there have been several reports of cerebral chagoma in AIDS patients.[7,8,9,10,11,12,13,14,15,16,17] The cases of cerebral chagoma non-related to AIDS found in our review are summarized in ►**Table 1**. Among patients immunosuppressed for causes other than AIDS, the following was found: 1 patient using methotrexate due to rheumatoid arthritis;[18] 2 patients with leukemia;[19,20] 2 patients undergoing kidney transplantation;[21,22] and only 1 reported case of a patient who underwent a heart transplantation,[4] similar to our case. Such a complication in heart transplant patients is very rare. In a series of 107 heart transplantations over 25 years, it occurred to only 1 patient,[23] the same case described by Marchiori et al.[4] We present 3 transplanted and biopsied cases in the same hospital with an interval of 5 years between them. Like the case described by Marchiori et al. (2007), the reactivation in the 3 cases of our sample occurred in the first 7 months after transplantation.

The best treatment for CD in immunocompromised patients is still uncertain, since the available data are limited to observational studies. Two medications are described as effective in reactivation treatment, benznidazole and nifurtimox. In all 3 cases described in this report, treatment with benznidazole at a dose of 5 mg/kg/day for 60 days was used.[25,26] The mortality rate in cases of CD reactivation in patients with HIV is ~ 79%, with an average survival time of 21 days.[7] On the other hand, in reactivation after heart transplantation, the behavior is apparently more indolent,

Table 1 Tumor-like Chagas disease reactivation cases non-related to acquired immunodeficiency syndrome

Author, year	Sex	Age (years)	Base disease	Symptoms	Site of lesion	Treatment
Queiroz,[6] 1973	M	62	T-cells lymphoma	–	–	No
Salgado,[19] 1996	M	76	Lymphocytic leukemia	Intracranial hypertension	Right Parieto-occipital	Benznidazole 5 mg/kg/day
Marchiori,[3] 2007	M	46	Cardiac transplant, 7m	Left hemiparesis, dysarthria, dysphagia	Right fronto-parietal	No
Cohen,[20] 2010	F	15	Lymphoblastic leukemia	Headache, fever	Left occipital	Benznidazole 7 mg/kg/day
Cicora,[21] 2014	M	27	Kidney transplant, 6y	Intense headache	Right frontal	Benznidazole 7 mg/kg/day
Montero,[22] 2018	M	62	Kidney transplant, 3y	Left arm paresis, bradypsychia	Corpus callosum	Benznidazole 15 mg/kg/day
Kaushal,[18] 2019	F	88	Rheumatoid arthritis	Right-sided weakness, slurred speech	Bilateral frontoparietal	No

since all patients described in our series are alive and only one patient has severe neurological sequelae.

Conclusion

Heart transplantation is considered the gold standard for the treatment of severe Chagas cardiomyopathy. Although more common in patients with AIDS-related immunosuppression, tumor-like reactivation in the central nervous system may happen in heart-transplant patients. Therefore, due the multiple differential diagnoses in this context, we believe that brain biopsy should be considered when feasible.

Conflict of Interests

The authors have no conflict of interests to declare.

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