Case Report: Meningoencephalitis Caused by Reactivation of Chagas Disease in Patient without Known Immunosuppression

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Abstract. Central nervous system (CNS) involvement in Chagas disease (CD) is an uncommon complication that can result from direct involvement of the parasite or from thromboembolic phenomena. Direct involvement of CNS can occur in both acute and chronic forms of CD, and can also be secondary to reactivation. Reactivation of CD generally occurs in immunosuppressed patients such as those with human immunodeficiency infection or malignancies being rarely described in patients without apparent immunosuppression. We report a case of a patient living for many years in a nonendemic area for CD that presented to the emergency department with sudden onset of neurological symptoms as a result of reactivation of the disease. The microorganism was isolated from cerebrospinal fluid, and despite appropriate use of benznidazole, the patient died of sepsis after 22 days of treatment. Further investigation did not show any apparent cause of immunosuppression. This case report shows the importance of considering the diagnostic possibility of neurological complications from CD reactivation in patients that have ever lived in CD-endemic areas even without apparent underlying immunosuppression.

INTRODUCTION

Chagas disease (CD) caused by *Trypanosoma cruzi* is a major public health problem in Latin American with 5.7 million people infected and nearly 100 million people at risk in endemic areas. CD is multisystemic disorder and can lead to cardiovascular, digestive, and central nervous system (CNS) dysfunction.^{1–6} Carlos Chagas described in 1911 the involvement of the nervous system in CD, based on histopathological studies.^{7,8}

Neurological involvement of CD can be defined as the finding of 1) trypomastigote in the direct examination of cerebrospinal fluid (CSF), 2) amastigotes in the histopathological analysis of brain tissue, or 3) trypomastigote in the direct examination of blood associated with neurological manifestations and clinical response after specific treatment.⁶

Neurological manifestations of CD differ according to the phase of infection.⁷ The acute phase is more commonly found in children under 2 years of age and presents as encephalitis invariably associated with myocarditis. In chronic CD, the involvement of the central and the peripheral nervous system is not frequent but may result in dementia, confusion, and neuritis. Reactivation of CD in chronically infected patients may result in neurological findings secondary to the presence of intracerebral mass lesions or acute diffuse meningoencephalitis.^{2,3,7} The patient usually develops fever, signs and symptoms of intracranial hypertension, focal deficits, progressive loss of consciousness, headache, and seizures.⁹ Neuroimaging scans reveal abnormalities in most patients and brain abscesses can be observed in up to 50% of cases.⁵ Single or multiple cerebral lesions are generally located in the subcortical white matter hemispheres.^{9,10}

Acute neurological reactivation of chronic CD was first reported in 1969 in a patient with chronic lymphocytic leukemia.⁷ In the following decades, the occurrence of such complication was more frequently observed due to the

increased use of immunosuppressants (e.g., steroids, anti-rejection drugs, chemotherapy) or in association with human immunodeficiency virus (HIV) infection.^{7,9,10} Approximately 75–80% of cases of neurological CD reactivation occur in patients with HIV infection. Since 2004, the reactivation of the disease is considered an HIV-related opportunistic infection.^{7,10}

The early diagnosis of neurological CD reactivation is crucial, considering that the disease has a high case fatality rate (up to 85%) and that prompt antiparasitic treatment has impact on clinical prognosis.^{5,7} Benznidazole at a dose of 5 mg/kg/day divided into two doses for 60 days is the treatment of choice.^{9,11}

Reports of neurological reactivation of CD in patients with no underlying immunosuppression are scarce in the literature.¹² Herein, we report a patient with no apparent immunosuppression that presented with meningoencephalitis caused by reactivation of CD.

CASE REPORT

A 57-year-old man was admitted to a local hospital with right hemiplegia and aphasia. The symptoms had a sudden onset 15 days before admission and were gradually worsening. The patient had no fever and did not report headache. The patient was born in the rural area of São Joaquim, Minas Gerais, Brazil, an endemic area for CD but was living in an area with no domiciliary transmission (Belo Horizonte, Minas Gerais) for the past 30 years. The patient had a history of hypertension and was taking nifedipine, captopril, and hydrochlorothiazide. A computed tomographic (CT) scan of the brain was performed at admission and showed a hypodensity on the right cerebral hemisphere with extrinsic compression of the right lateral ventricle and extensive hypodensity in frontoparietal white matter without significant uptake of iodinated contrast (Figure 1). A lumbar puncture was performed and revealed a clear CSF with a white cell count of 45 cells/mm³ (all mononuclear) without red blood cells, glucose level of 55 mg/dL, and protein level of 85 mg/dL. Microscopic analysis revealed the presence of flagellate protozoa suggestive of *T. cruzi* (Figure 2). Serological tests for HIV and syphilis were negative. The CD4

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FIGURE 1. A computed tomographic scan of the brain evidencing a hypodensity on the right cerebral hemisphere with extrinsic compression of the right lateral ventricle.

cell count was 480 cells/mm³, and the level of total immunoglobulins was within the normal range. Chest radiograph showed cardiomegaly, and a chest CT scan showed a dilated esophagus with no evidence for pathological mediastinal or hilar lymphadenopathy. Lung parenchyma demonstrated no nodule, infiltrate, mass, consolidation, or atelectasis. Abdominal CT scan revealed three non-specific hypoattenuating hepatic nodular lesions in liver segments II and IV measuring between 5 and 9 mm. Electrocardiographic exam showed nonspecific ST-T wave

FIGURE 2. *Trypanosoma cruzi* (indicated by arrows) in the cerebrospinal fluid.

abnormalities without bundle branch block. Benznidazole 5 mg/kg/day was started 10 days after admission. Two days after admission, the patient developed hemodynamic instability, fever, and somnolence, requiring mechanical ventilation. Piperacillin/tazobactam was started for a presumed diagnosis of pulmonary sepsis. Twenty days after the beginning of the treatment, the patient was still comatose, despite normalization of CSF abnormalities and the reduction of cerebral edema as assessed by a brain CT scan. On the 22nd day of treatment, he developed a new pulmonary sepsis caused by a multidrug-resistant germ (meropenem-resistant *Acinetobacter baumannii*). Death occurred after 39 days of admission and 50 days after disease onset.

DISCUSSION

We reported a case of neurological reactivation of CD in a patient without an identifiable immunosuppressive condition. CD is still one of the most important endemic infections of the Americas.¹¹ The neurological manifestations of CD reactivation depend primarily on the location, size, and number of lesions, which can vary. In a study of 15 patients coinfecting with HIV and CD confirmed in the CNS, the most frequent clinical findings were headache, focal deficits, fever, seizures, and sensorial loss.⁵ The finding of hemiplegia, aphasia, and sensorial loss in our case probably reflects the effects of the cerebral mass lesion that was observed in the CT scan. In addition to the neurological symptoms, fever is another very frequent manifestation, although it was not reported by our patient.⁷ Neurological signs and symptoms of CD can be similar to those from other causes of encephalitis, such as neurotoxoplasmosis, and therefore require a high level of suspicion.⁶

Subcortical hypodense and involvement of the white matter is common in head CT scan, although it can be normal in some patients.⁷ Encephalitis can result in necrosis and edema, which can lead to mass effect with midline shift such as the one observed in our patient.³ The frontoparietal involvement seen in the CT scan was probably responsible for the observed aphasia, suggesting left hemisphere dominance, and the lateral ventricle compression with indirect involvement of the basal ganglia resulted in hemiplegia. Unfortunately, a brain MRI that could have better explained the patient's neurological manifestations was not performed.

The diagnosis of the case was only possible after the lumbar puncture that was not readily performed because of the risk of cerebral herniation. The biochemical profile of the patient's CSF was consistent with those reported in the literature: lymphocytosis, with high protein, and the presence of *T. cruzi* by direct examination.^{1,2,6-9,13} Noteworthy, in most cases the identification of the parasite requires Giemsa staining of CSF, which was performed in our case and confirmed the preliminary finding on direct examination.⁷

Although serological tests for CD were not performed in our case, the positive serology finding is important for the diagnosis of neurological disease reactivation, although not essential. Serological tests in such cases show positivity of 86%, but if negative, the possibility of the disease should not be excluded, especially in people who inject drugs, where negative serology is commonly found.^{3,5,6} The finding of dilatation of the distal esophagus on chest CT probably

represents esophageal involvement of CD, which suggests that the patient had a reactivation of a chronic infection.

Neurological reactivation of CD can occur in the context of immunosuppression, although uncommon.⁴ In a review of 100 years of neurological involvement of CD, all of the 180 patients described had underlying immunosuppression (130 had acquired immune deficiency syndrome [AIDS], 41 had previous organ transplant, 10 had leukemia or Hodgkin's lymphoma, and one had hypogammaglobulinemia).⁷ According to Pittella, all patients with AIDS and reactivation of the disease in the CNS had lymphocyte count CD4⁺ less than 200 cells, with a high mortality rate.⁷ However, there is at least one report of a patient with CD meningoencephalitis not related to immunosuppression.¹² In our case report, the patient had a negative HIV serology, undetectable HIV viral load, CD4 cell count of 480 cells/mm³, normal total immunoglobulin levels, and no clinical or radiographic evidence of cancer. Unfortunately, we could not perform a longitudinal assessment of CD4 cell count and immunoglobulin levels due to the unfavorable clinical course of our patient.

As defects in cellular immunity usually predispose individuals to fungal, protozoan, or mycobacterial infections, one would expect to find some cellular immunodeficiency in the reported patient, which was not confirmed with the available laboratory tests.¹¹ Cancer has also been associated with reactivation of CD, but we could not find any evidence for solid or hematological neoplasia in our patient.¹⁰ Abdominal CT scan revealed small liver lesions that could not be precisely characterized. Such liver findings often represent small cysts that are common in the general population and are not suggestive of liver metastasis.

The use of benznidazole is recommended for the management of neurological manifestations of CD.^{9,11} Unfortunately, our patient died despite using antiparasitic therapy. In 1999, Pagano and others³ described 10 cases of HIV-associated neurological reactivation of CD of whom only one survived for more than 1 year after the diagnosis. In a study conducted in 2008 by Cordova and others with a similar group of patients, the average survival time after diagnosis of the 15 studied patients was 21 days, with an 80% case fatality rate.^{3,6}

Finally, it is noteworthy that although being born in an area endemic for CD, the patient has been living in an area with no domiciliary transmission for many decades. Although a new infection could not be completely ruled out, it is quite unlikely and highlights the importance of obtaining a precise history of patient's previous place of residence.^{5,6}

Although uncommon, this case report shows that CD reactivation with CNS involvement can occur in a patient without overt underlying immunodeficiency.

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