CASO CLÍNICO / *CLINICAL CASE*

Histoplasmose do Sistema Nervoso Central em um doente com Síndrome da Imunodeficiência Adquirida: Diagnóstico Diferencial em Áreas Endêmicas

Central Nervous System Histoplasmosis in a patient living with Acquired Immunodeficiency Syndrome: Differential Diagnosis in Endemic Areas

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/ Resumo

Este relato de caso descreve a dificuldade em fazer o diagnóstico de neurohistoplasmose em um paciente com Vírus da Imunodeficiência Adquirida (HIV). O envolvimento neurológico nos casos de histoplasmoses é raro, aparecendo quando há um comprometimento expressivo da imunidade. Essa patologia está associada a uma alta morbidade e mortalidade, sendo um diagnóstico diferencial importante em pacientes com HIV e sintomas neurológicos, especialmente em áreas endêmicas para *Histoplasma Capsulatum*.

Palavras-chave: Hipertensão intracraniana; HIV/AIDS; Anfotericina B desoxicolato

/ Abstract

This report describes a difficult diagnosis of neurohistoplamosis in a patient living with Human Immunodeficiency Virus (HIV). Neurological involvement in cases of histoplasmosis is rare and usually happens when the immune system is compromised. This disease has high morbidity and mortality, and as such is an important differential diagnosis in HIV patients with neurological symptoms, especially in areas where the fungus **Histoplasma capsulatum** *is endemic.*

Keywords: *Intracranial hypertension; HIV/AIDS; Amphotericin B Deoxycholate*

/ Introduction

Histoplasmosis is a fungal disease caused by *Histoplasma capsulatum*, a dimorphic fungus endemic in many areas in the world. *H. capsulatum* is commonly found in its mycelial form in soils with high nitrogen content, such as chicken coops and bat caves [1,2]. Humans are infected by inhalation of the mycelial form, which turn into a yeast once it reaches the lungs, and are phagocytosed by macrophages, with potential dissemination throughout the body [3].

Risk factors for disseminated histoplasmosis at any age include large inoculum exposure and acquired immunodeficiency resulting from use of immunosuppressive agents, malnutrition, or human immunodeficiency virus (HIV) infection, particularly those individuals with a CD4-lymphocyte count below 150 cells/mm^3 [4].

The infection of the Central Nervous System (CNS) by *H. capsulatum* can happen in 10-20% of the cases that progresses to the disseminated form, can occur in subacute or chronic forms, with the duration of symptoms ranging from two months to many years [5,6].

The diagnosis can be quite challenging because it has a clinical scenario similar to many other CNS diseases (neurotoxoplasmosis, CNS metastasis, bacterial abscesses, neurotuberculosis and others)[7]. Its mortality rate is about 30% but it can reach up to 60% when associated with AIDS, necessitating a long course of treatment with risk of relapses [5].

This report describes a case of neurohistoplasmosis in a patient living with HIV, who was also being treated for disseminated tuberculosis (TB).

/ Case report

A 40-year-old male sought our service in March 2019 complaining of 4 months of dizziness that progressed to ataxic gait, balance and postural disturbances, diplopia, holocranial headaches, retro-orbital pain, nausea and vomiting for about one month. The patient was a worker at a chicken farm that was occasionally visited by bats in the city of Goiânia-GO (Central-West Brazil).

His previous medical record is notable for HIV and active TB diagnosed in 2017. He completed tuberculosis treatment but stopped using Antiretroviral Therapy (ART) until November 2018, when he was diagnosed with TB again. At that time, his CD4-lymphocyte count was 21 cells/mm^3, and viral load was 424.082 copies/mL.

In January 2019, the patient was diagnosed with disseminated histoplasmosis confirmed by *H. capsulatum* identification in blood culture. He was treated with a 14-day course of amphotericin B deoxycholate and received long-term maintenance therapy with Itraconazole.

In March 2019, when he was admitted to our service with Glasgow Coma Scale score of 15 points, isochoric and photoreactive pupils, cerebellar gait, paresthesia in the left hand and no meningeal irritation signs. A cranial computed tomography (CT) scans showed multiple hypodense areas in the subcortical white matter in the deep frontoparietal region, bilateral ganglion-capsular region, and right temporal lobe, some of them with contrast enhancement. His Cerebrospinal fluid (CSF) analysis showed 8 cells/mm^3, glucose of 40 mg/dL (blood glucose: 110 mg/dL), protein levels of 117 mg/dL and Adenosine Deaminase (ADA) of 2,7 IU/L. Gram and Ziehl-Neelsen staining were negative, and mycobacteria, fungi and bacteria cultures were all negative as well. Serum VDRL was 1:32 and empiric treatment for suspected neurotoxoplasmosis was started with trimethoprim/sulfamethoxazole and aqueous crystalline penicillin for possible associated neurosyphilis. Then CSF analysis with polymerase chain reaction (PCR) for toxoplasmosis and JC virus, FTA-ABS and CSF-VDRL all presented negative results.

Magnetic resonance imaging (MRI) showed multiple nodular enhancing lesions with perilesional edema, randomly distributed throughout the brainstem, cerebral and cerebellar hemispheres (Figure 1). Dexamethasone was then started for 14 days leading to improvement of clinical symptoms and hospital discharge.

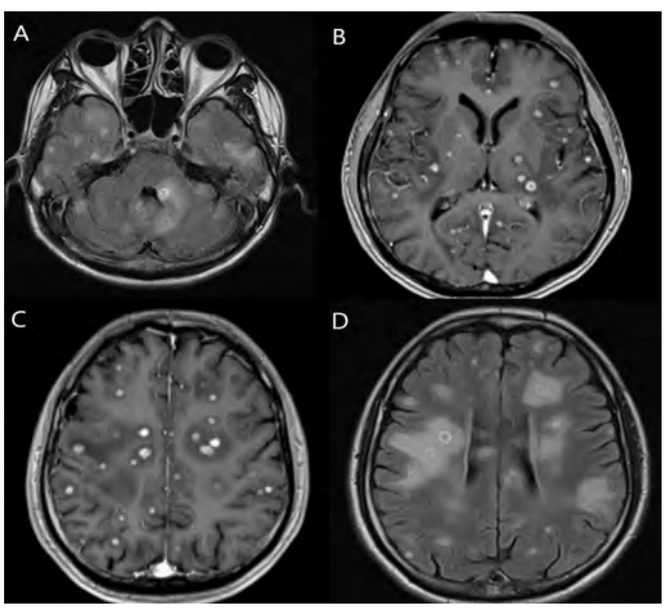

Figure 1 – High-field Nuclear Magnetic Resonance images. A: Axial section in FLAIR (fluid-attenuated inversion recovery) sequence showing multiple rounded nodular lesions with annular enhancement and perilesional edema, distributed on the temporal lobes, cerebellum and left cerebellar peduncle. B and C: Axial section in T1 sequence after use of paramagnetic venous contrast with gadolinium showing rounded nodular lesions, with predominantly annular enhancement, moderate perilesional edema on the brain hemispheres. D: Axial section in FLAIR demonstrating perirolandic region with multiple rounded nodular lesions with surrounding edema in the parenchyma of bilateral brain hemispheres, predominating in the periventricular regions.

However, in May 2019, 7 days after discharge, the patient's neurological condition deteriorated (Glasgow Coma Scale score of 13) and he was readmitted with neck stiffness, positive Kerning´s sign, nystagmus in the right eye and dysarthria. At this time, CSF opening pressure was 40 cmH_2O and reveled increased protein (194 mg/dL) and cellularity (65 cells/mm^3) with predominance of lymphocytes (99%), glucose consumption (37 mg/dL, blood glucose:170 mg/dL), and isolation of *H. capsulatum* from CSF culture (Figure 2). Amphotericin B Deoxycholate was given for 6-weeks, with repetitive therapeutic lumbar punctures performed until opening pressure was normalized after 14 days. The patient showed complete improvement in dizziness and visual disturbances, and had also significant progress in gait and balance. New MRI (Figure 3) demonstrated substantial reduction in nodular lesions and perilesional edema.

/ Discussion

The literature related to the CNS manifestations of histoplasmosis is diverse. Nonetheless, some studies show that certain clinical aspects are more common than others, with meningeal involvement being the most common, characterized by decreased level of consciousness, headaches, cranial nerve involvement, seizures, confusion, neck stiffness and photophobia. These clinical features, despite being the most common ones, may be preceded by several other nonspecific clinical manifestations, which characterizes histoplasmosis with CNS involvement as a chronic disease with periods of exacerbation [8,9].

Other clinical features found in the literature are cognitive impairment, ataxia, vertigo and even stroke [6,9]. It is significant to notice that the patient from our case presented with vertigo, imbalance and unsteady gait months before presenting with the typical manifestations of meningitis, indicating a chronic condition that acutely progressed to the meningeal form.

Although CNS involvement by *H. capsulatum* may occur in immunocompetent individuals, it is much more common among those with some degree of immunosuppression like diabetes, steroid use, solid organ transplants, neoplasia, extremes of ages, but especially in individuals with AIDS [3].

About 90% of cases of CNS histoplasmosis present alterations in imaging, making CT scans and MRI an indispensable part of the diagnostic investigation [3]. A retrospective multicenter study, with 77 patients with confirmed diagnosis of CNS histoplasmosis by CSF culture, showed that 72% of patients had imaging abnormalities, with 4 patients showing abnormal imaging only on MRI. The imaging findings of their sample were diverse, with 20% of the patients presenting with focal mass lesions, and 17% presenting with multiple lesions [10].

The most common radiological finding in CNS histoplasmosis is the presence of multiple lesions with peripheral enhancement with contrast, a nonspecific sign that must direct us to a list of differentials including neurotoxoplasmosis, metastases, bacterial abscesses, fungal abscesses, neurocysticercosis abscess, neurotuberculosis, glioblastoma and even diseases like Lupus and Whipple's disease [11]. In addition to these more frequent findings,

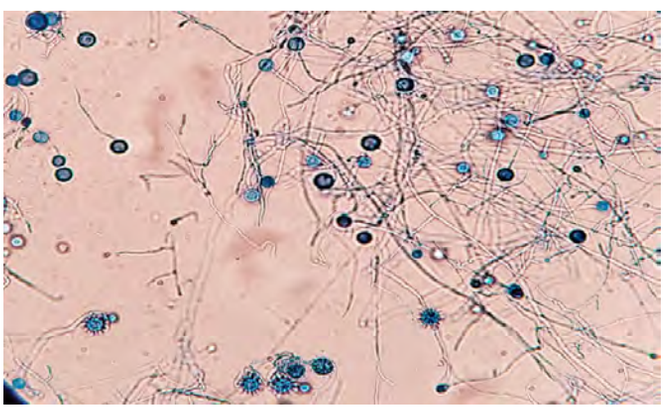

Figure 2 – Cerebrospinal fluid culture showing tuberculate, unicellular, spiculated and rounded macroconidia measuring 8 to 14µm (stalagmospores) formed in short, hyaline and undifferentiated conidiophores, typical of *Histoplasma capsulatum*.

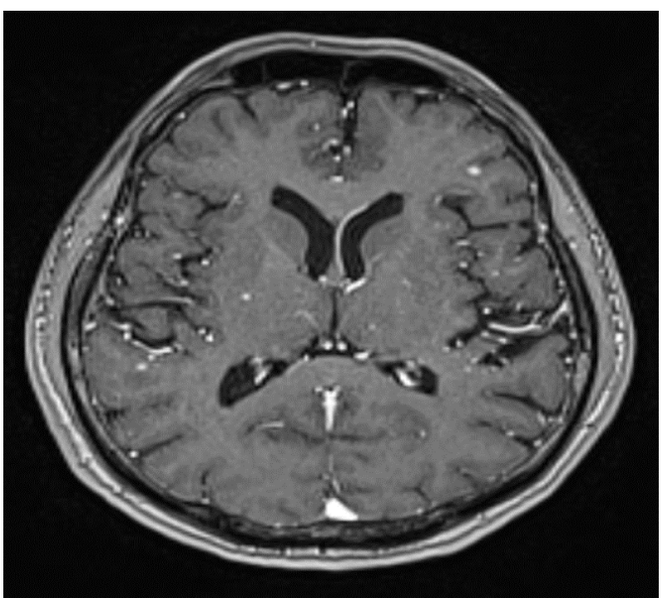

Figure 3 – High-field Nuclear Magnetic Resonance imaging. Axial section in T1 sequence demonstrating reduction of brain lesions after treatment for neurohistoplasmosis.

other abnormalities include meningeal thickening, calcifications, spinal and vascular injuries [6].

It is particularly challenging to confirm the diagnosis of neurohistoplasmosis. CSF culture remains the gold standard, however, it has low sensitivity for the detection of histoplasma. Likewise, cultures can take up to six weeks to grow, delaying diagnosis and treatment with catastrophic consequences and, due to the severity of neurohistoplasmosis, many patients may die even before results arrive [7,11,12].

Aiming to minimize this burden, recent studies have been focusing on the detection of antigens and antibodies for histoplasma in the CSF via immunoenzymatic assays, which have been showing higher sensitivity (98%) and specificity (90%), and the ability to decrease time for diagnosis and treatment [7].

In our case, it took 21 days for the patient's CSF culture to produce positive results. Previously, the patient had already had three CSF analyses with negative cultures for fungi. The CSF culture was only able to identify the pathogen when the patient developed the meningeal form of the disease, but even before, he had already presented other neurological symptoms. This fact highlights the limitations of CSF culture for the diagnosis of neurohistoplasmosis, especially in cases where there is no meningeal involvement.

Also noteworthy is the fact that even before isolating the pathogen in the CSF, the patient was found to have disseminated histoplasmosis, with a positive blood culture for *H. capsulatum*. This fact should be valued as it could indicate that his previous neurological involvement could be caused by *H. capsulatum*, which enabled empiric treatment, as it is common practice with several other serious diseases involving AIDS patients.

The latest guidelines from the Infectious Diseases Society of America (IDSA) [4], on CNS histoplasmosis states that its treatment should be done with Liposomal Amphotericin B at a dose of 5 mg/kg/day during 4 to 6 weeks, with a maximum dose of 175 mg/kg. This should be followed by a maintenance phase with Itraconazole 200 mg, 2 to 3 times a day, during at least 1 year and until normalization of the CSF, with negative testing for histoplasma antigen in the CSF, and in the case of HIV patients, until CD4 count is greater than 150 cells/mm^3. It is also advised to monitor serum drug levels, in order to confirm the therapeutic efficacy for CNS penetration. Although the recommended drug of choice is Liposomal Amphotericin B, because of less adverse effects and greater penetration into the CNS, in many places of Brazil, access to this medication is limited due to its high cost. In our study the patient was treated with Amphotericin B Deoxycholate and was able to continue treatment for only 5 weeks, instead of 6, due to the development of acute renal failure. The patient continued being monitored in an outpatient setting, using Itraconazole for maintenance.

In conclusion, although neurological involvement in histoplasmosis is rare, it should be included in the differential diagnosis of neurological conditions in individuals with HIV/AIDS, especially those from endemic regions. Early and accurate diagnosis are essential for proper treatment, ensuing a reduction in disease morbidity.

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/ References

1. Manos NE, Ferebee SH, Kerschbaum WF. Geographic variation in the prevalence of histoplasmin sensitivity. Dis Chest. 1956;29(6):649–68.

2. Armstrong PA, Jackson BR, Haselow D et al. Multistate epidemiology of histoplasmosis, United States, 2011–2014. Emerg Infect Dis. 2018;24(3):425–31.

3. Medoff G, Kobayashi GS, Painter A, Travis S. Morphogenesis and pathogenicity of *Histoplasma capsulatum*. Infect Immun. 1987;55(6):1355–8.

4. Wheat LJ, Freifeld AG, Kleiman MB et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45(7):807–25.

5. Wheat LJ, Batteiger BE, Sathapatayavongs B. *Histoplasma capsulatum* infections of the central nervous system: a clinical review. Med (United States). 1990;69(4):244–60.

6. Machado LR, Nóbrega JP, Livramento JA, Vianna LS, Spina-França A. Histoplasmosis of the central nervous system. Clinical aspects in 8 patients. Arq Neuropsiquiatr. 1993;51(2):209–12.

7. Bloch KC, Myint T, Raymond-Guillen L, Hage CA et al. Improvement in diagnosis of Histoplasma meningitis by combined testing for Histoplasma antigen and immunoglobulin G and immunoglobulin M anti-Histoplasma antibody in cerebrospinal fluid. Clin Infect Dis. 2018;66(1):89–94.

8. Trofa D, Nosanchuk JD. Histoplasmosis of the central nervous system. J Neuroparasitology. 2012;3(7):1–7.

9. Loughan AR, Perna R, Hertza J. Cognitive impairment and memory loss associated with histoplasmosis: a case study. Clin Neuropsychol. 2014;28(3):514–24.

10. Wheat LJ, Myint T, Guo Y, Kemmer et al. Central nervous system histoplasmosis: multicenter retrospective study on clinical features, diagnostic approach and outcome of treatment. Med (United States). 2018;97(13):e0245.

11. Gonzalez HH, Rane M, Cioci A, Goodman S, Espinosa PS. Disseminated central nervous system histoplasmosis: a case report. Cureus. 2019;11(3):e4238.

12. Hage CA, Ribes JA, Wengenack NL et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. Clin Infect Dis. 2011;53(5):448–54.