Diagnosing Ring-Enhancing Lesions in the Brain of a Patient With AIDS Without Brain Biopsy: A Case of Central Nervous System Histoplasmosis

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Abstract

We report a case of a Puerto Rican male with advanced AIDS who presented with multiple falls and pancytopenia. Magnetic resonance imaging (MRI) of the brain, as initial workup, revealed 2 ring-enhancing brain lesions. Initial cerebrospinal fluid analysis revealed minimal cells, mildly elevated protein, and no organism seen on gram stain. Due to prohibitive thrombocytopenia, brain biopsy was deferred. He had neither clinical nor radiographic improvement despite empiric therapy for both toxoplasmosis and bacterial abscesses. Indicated by pancytopenia, bone marrow (BM) aspiration was performed. Culture of BM aspirate grew *Histoplasma capsulatum*. Urine histoplasma antigen was markedly elevated. He was treated with liposomal amphotericin B (LamB) for progressive disseminated histoplasmosis with probable central nervous system involvement. Cerebrospinal fluid histoplasma antigen obtained after 2 months of LamB was detected. After prolonged course of LamB, he took itraconazole. Brain MRI at 7-month follow-up revealed significant improvement from baseline study.

Keywords

histoplasmosis, AIDS, central nervous system fungal infections, central nervous system infections, brain abscess, central nervous system infections, diagnosis

Background

Histoplasmosis is an infection caused by a dimorphic fungus *Histoplasma capsulatum*. In the continental United States, *Histoplasma capsulatum* is endemic to the central and eastern states. Outside of this area, it is endemic to Puerto Rico, the Caribbean Islands, and Central America. The extent of the disease depends on inhaled conidia and the host's cellular immune response.¹ Individuals living in endemic areas can develop progressive disseminated histoplasmosis (PDH) shortly after initial exposure. On the other hand, individuals in nonendemic areas can develop PDH after reactivation of latent infection acquired from prior travel or residence in endemic areas.²

Although disease can occur in immunocompetent individuals, the presentation of histoplasmosis is typically more severe and more likely to disseminate in the immunocompromised host. Histoplasmosis is an opportunistic infection and has significant morbidity and mortality among patients with AIDS. Progressive disseminated histoplasmosis can be the initial presentation of HIV/AIDS in patients without antiretroviral therapy (ART).³ HIV patients with CD4 counts

<150 cells/mm³ are at greatest risk of PDH. It has been previously reported that 3% to 5% of patients with AIDS in endemic areas of North America had PDH.⁴ Reactivation of latent infection is rare and most commonly occurs in individuals with CD4 counts less than 150 cells/mm³.⁵ Up to 10% of those with disseminated disease can have central nervous system (CNS) involvement.⁵ More commonly, CNS histoplasmosis presents as meningitis. However, it can also present as discrete, focal granulomas called histoplasmoses. A histoplasmosis can be either a caseating or noncaseating

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Figure 1. Magnetic resonance imaging (MRI) done at admission at referring hospital. A, Diffusion-weighted imaging (DWI). B, Apparent diffusion coefficient (ADC). C, T1 post-contrast. D, Fluid-attenuated inversion recovery (FLAIR). E, T1 postcontrast. F, T2. (A) and (B) Restricted diffusion of the larger corpus callosal lesion, (C) postcontrast T1-weighted image shows enhancement of the smaller insular lesion, and (D) FLAIR shows mild edema surrounding the corpus callosal lesion. Also seen, severe white matter changes consistent with HIV leukoencephalopathy, (E) postcontrast T1-weighted image showing ring-enhancing lesion in the body of the corpus callosum, and (F) T2-weighted image reveals a predominantly hypointense lesion with an irregular rim, which has been described in fungal abscess.

granuloma on histology⁶ and can appear as ring-enhancing brain lesion on magnetic resonance imaging (MRI),⁷ similar to bacterial abscess, toxoplasmosis, or lymphoma. Because of the high mortality, estimated at 20% to 40% among patients with CNS histoplasmosis,⁸ it is important to recognize this as a potential cause of ring-enhancing lesions in immunocompromised host with a known history of exposure.

Case Report

A 55-year-old male originally from Puerto Rico with AIDS ($CD4 = 5 \text{ cells/mm}^3$) was transferred to our institution from a community hospital for workup of ring-enhancing brain lesions. At the referring hospital, he was admitted twice due to frequent falls a month apart. During his first admission, he was febrile and workup was remarkable for pancytopenia, mildly elevated alkaline phosphatase 113 U/L, and elevated lactate dehydrogenase (LDH) 709 U/L. Cerebrospinal fluid (CSF) obtained by lumbar puncture (LP) revealed 2 mononuclear cells and mildly elevated protein (63 mg/dL). Computed tomography (CT) of the head demonstrated white matter changes consistent with chronic small vessel ischemia. He left against medical advice and returned 1 month later due to repeated falls at home. Per review of his medical records, he had fever, orthostasis, cachexia, and oral thrush. Neurologic examination was essentially normal. He still had pancytopenia

(platelets $23 \times 1000/\mu\text{L}$, white blood cell [WBC] count $2.9 \times 1000/\mu\text{L}$, hemoglobin 8.2 g/dL) and both alkaline phosphatase and LDH were increased compared to prior hospitalization (229 and 2388 U/L, respectively). Magnetic resonance imaging of the brain revealed 2 ring-enhancing lesions: a 3-cm lesion with restricted diffusion in the body of the corpus callosum and an 8-mm lesion in the insula (Figure 1). Serum toxoplasma antibody (IgG) was negative. Highly considered in the differential were CNS toxoplasmosis, lymphoma, and brain abscess. He was treated empirically for toxoplasmosis with pyrimethamine, sulfadiazine, and leucovorin.

On hospital day (HD) 5, bone marrow (BM) biopsy was performed due to fever and pancytopenia. The BM was hypocellular with focal serous atrophy, and stains were negative for malignant cells, fungi, and acid-fast bacilli (AFB). Routine bacterial, AFB, and fungal cultures were sent out to a reference laboratory and all returned negative. Due to gastrointestinal intolerance, his toxoplasmosis treatment was changed to clindamycin, pyrimethamine, and leucovorin. He remained febrile which, prompted repeat LP on HD 9. Cerebrospinal fluid results were the following: WBC count of $0/\text{mm}^3$, red blood cell count of $0/\text{mm}^3$, glucose of 38 mg/dL, and protein of 72 mg/dL. Cerebrospinal fluid polymerase chain reactions (PCRs) for Epstein Barr virus and *Toxoplasma gondii* were low-level viral copies and undetectable, respectively. Repeat MRI brain

Figure 2. Magnetic resonance imaging (MRI) done 7 months after antifungal treatment initiation. A, Diffusion-weighted imaging (DWI). B, Apparent diffusion coefficient (ADC). C, T1 post-contrast. D, Fluid attenuated inversion recovery (FLAIR). E, T1 postcontrast. F, T2. (A) and (B) show persistent diffusion restriction, however, lesion size is decreased, (C) post contrast T1-weighted image shows enhancement of the smaller insular lesion, (D) FLAIR imaging with absent surrounding edema, (E) T1 postcontrast study shows persistent enhancement, however, lesion is at least 50% smaller, and (F) T2-weighted sequence shows the residual T2 hypointense rim but without the central region of T2 prolongation.

on HD 9 revealed a slight increase in edema surrounding the larger corpus callosum lesion.

He was transferred to our institution on HD 17. On arrival, his physical examination was only notable for thrush, which prompted treatment with fluconazole. Brain biopsy was deemed high risk by neurosurgery due to thrombocytopenia refractory to platelet transfusion. A consensus was reached among consultants and the primary team to empirically treat for both CNS toxoplasmosis and bacterial abscess. Urine histoplasma antigen was sent as part of the workup for pancytopenia. In order to address the likelihood of CNS lymphoma, fludeoxyglucose (FDG)—positron emission tomography scan of the brain was performed and showed no FDG avidity.

On HD 29 (12th HD in our institution), the BM fungal culture was reported to have growth. The following day, urine histoplasma antigen returned positive and elevated beyond the test threshold. He was immediately started on conventional amphotericin B. Amphotericin B was started on day 14 of fluconazole treatment for oral thrush. On HD 35, the fungal growth in BM culture was confirmed *Histoplasma capsulatum* by DNA probe. Due to high suspicion for PDH with CNS involvement, treatment was switched to liposomal amphotericin B (LamB) and the therapies for toxoplasmosis and brain abscess were discontinued. Repeat MRI of the brain after 5 weeks of amphotericin B demonstrated decreased size of lesions, though surrounding edema was unchanged. *Histoplasma* PCR of stored CSF sample obtained on HD 1 was sent

out to a reference laboratory. This was later reported nondetectable. On HD 41, he was started on ART comprised of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate. He was later discharged to a long-term care facility to complete induction treatment of LamB. Toward the end of induction, he was readmitted to another hospital due to fever. Workup of fever included CT of the chest, which revealed a right upper lobe mass that was subsequently biopsied. Pathology was significant for noncaseating granulomatous pneumonitis, suspected to be due to histoplasmosis in the setting of immune reconstitution inflammatory syndrome (IRIS) while on ART. Fungal cultures were negative. A repeat LP was performed, and CSF was positive for *histoplasma* antigen (0.48 ng/mL). His serum *histoplasma* antigen was detectable and elevated at 13.45 ng/mL. After receipt of 122 days (23, 290 mg) of LamB therapy, he was later transitioned to oral itraconazole. Repeat MRI of the brain at 7 months from the first MRI revealed marked improvement (Figure 2).

Discussion

Central nervous system histoplasmosis can occur in 5% to 10% of PDH⁹ and has a range of clinical presentations including acute and chronic meningitis, vasculitis with stroke, encephalitis, myelopathy, and focal brain lesions (histoplasma).¹⁰ The most common presentation of CNS histoplasmosis is basilar meningitis, which can be complicated by hydrocephalus.¹

Histoplasmosis has been increasingly reported in the literature as a cause of focal CNS infection.¹¹⁻¹⁷ Central nervous system involvement may be part of disseminated disease or it can be an isolated presentation, which could be either the initial presentation of PDH or a relapse of previous CNS infection.¹⁸

Histoplasmosis should be highly considered in the differential of brain parenchymal lesion when the patient has known exposure to endemic areas. Definitive diagnosis of isolated intracranial histoplasmosis requires brain tissue for histopathology and culture¹⁹; however, this might not be an option in situations that preclude brain biopsy, as illustrated by our case (ie, prohibitive thrombocytopenia). Multiple noninvasive and nonculture-based tests may be utilized in cases where biopsy is not feasible.^{20,21} If there is associated meningitis with CNS histoplasmosis, the CSF should reflect the characteristic elevation in WBC count, elevated protein, and low glucose. Cerebrospinal fluid can be bland in the absence of meningitis and CSF WBC count may be normal in the setting of severe leukopenia. Cerebrospinal fluid culture is not an ideal diagnostic test due to its low sensitivity, ranging from 27% to 65%; however, sensitivity increases as sample volume increases (>10 mL CSF).¹⁸ The CSF PCR has not been validated for the diagnosis of histoplasmosis with standard methods; thus, it is not recommended at present to be used in patients suspected to have CNS histoplasmosis.¹⁸ Histoplasma antigen testing of the CSF has a reported sensitivity of 38% in all patients but has better sensitivity of 67% in patients with AIDS.^{2,5}

The diagnosis may be easily obtained in patients with PDH because other peripherally infected sites can be easily sampled for culture and histopathology. Cultures of blood and BM were reported to be highly specific (100%) but have limited sensitivity of 54% and 33%, respectively.¹⁸ Urine histoplasma antigen has a sensitivity of 92% and serum antigen has a sensitivity of 82% among all patients with PDH.²¹ Sensitivities of the tests are better in patients with AIDS (95% for urine and 86% for serum).²¹

Treatment of CNS histoplasmosis is challenging and based on relatively few case reports of meningitis.¹⁸ Central nervous system histoplasmosis does not respond as well as non-CNS histoplasmosis to antifungal therapy.²² Current guidelines recommend induction therapy with LamB (5.0 mg/kg daily for a total of 175 mg/kg given over 4 to 6 weeks) followed by itraconazole (200 mg 2 or 3 times a day) for at least 1 year. Liposomal amphotericin B is generally preferred over amphotericin B lipid complex or conventional amphotericin B due to its enhanced CNS penetration. However, the Infectious Disease Society of America guidelines stated that there is no available data to support this recommendation for CNS histoplasmosis. Treatment duration of amphotericin B may be extended in patients with large fungal burden, pancytopenia, or meningitis.²⁰

Itraconazole achieves lower CSF levels than fluconazole but was more effective in an animal model of CNS histoplasmosis.^{23,24} High-dose fluconazole is better tolerated than itraconazole but has a known risk of treatment failure.²⁵ Combination therapy of amphotericin B and an azole drug failed to show

improved outcomes compared to amphotericin B alone; therefore, it is not recommended.²⁴ Due to insufficient evidence, azole therapy alone without induction therapy with amphotericin B is not recommended for CNS histoplasmosis.²⁰

Urine histoplasma antigen can be used to assess treatment response. Antigen level declines with treatment and a rise in antigenuria should alert physicians of possible treatment failure.²¹ Patients with AIDS having antigenuria above 2.0 ng/mL at 1-year follow-up were 12.82 times more likely to relapse compared to those with antigenuria below 2.0 ng/mL.²⁶ A high relapse rate of close to 15% has been reported in patients with AIDS having CNS histoplasmosis.²⁶ It is thought that high relapse rate may be secondary to noncompliance, and therefore, therapeutic drug monitoring is required to ensure adequate drug exposure while on itraconazole therapy. In cases of progression of brain or spinal cord lesions despite antifungal therapy, surgery may be recommended.²⁰

Institution of ART is warranted to improve outcomes of HIV, especially in the setting of an opportunistic infection, but it can also induce IRIS. Immune reconstitution inflammatory syndrome is an enhanced cell-mediated immunity response toward a particular pathogen resulting to an exaggerated inflammatory reaction.²⁷ This may result in paradoxical worsening of histoplasmosis in spite of antifungal therapy or unmasking of a latent histoplasmosis infection.²⁸⁻³⁰ The histological finding of right upper lung lobe granulomatous inflammation in our patient observed during his treatment course on ART was compatible with T-cell-dependent macrophage activation restoration that occurs with IRIS.³¹ The management of IRIS is predominantly supportive; however, in the event of life-threatening inflammation, corticosteroids may be necessary.³²

In conclusion, CNS histoplasmosis is an emerging cause of brain parenchymal lesions among immunosuppressed hosts, such as patients with AIDS, with recent exposure or history of exposure to endemic areas of *Histoplasma capsulatum*. In patients living in nonendemic areas, CNS histoplasmosis likely represents reactivation of a latent infection that could occur in the setting of significantly depressed cell-mediated immunity. Appropriate diagnostic testing should be pursued either by indirect, noninvasive tests (such as histoplasma antigen), or tissue biopsy, so antifungal therapy can be initiated promptly, thereby decreasing morbidity and mortality.

Authors' Note

R. Beekman contributed to drafting the article, data collection, analysis and interpretation of data, and approval of the article. J. Hu contributed to drafting the article, critical revision of article, and approval of the article. S. Aronin contributed to critical revision of the article and approval of the article. M. Malinis contributed to critical revision of the article and approval of the article. This study was performed without any commercial funding.

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Declaration of Conflicting Interests

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