Central Nervous System Histoplasmosis in Acquired Immunodeficiency Syndrome

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ABSTRACT

Background: Involvement of the central nervous system (CNS) by *Histoplasma capsulatum* in AIDS is uncommon and not easily recognized.

Materials and Methods: CNS histoplasmosis cases from our institution were identified by a retrospective chart review from 2004-2014. A thorough literature search was performed for additional cases and their characteristics were compared. Clinical findings, treatment and outcomes are discussed.

Results: A total of 5 cases from our institution were identified. They had a clinical presentation that included classic signs of meningitis, often with evidence of disseminated involvement, and was typically severe with important neurological impairment. These cases were treated with antifungal agents, including a lipid amphotericin B formulation and azole drugs, but eventually 3 experienced nonresolution of their disease likely because of lack of adherence to therapy and died from their infection. The clinical presentation, treatment and outcome of these cases did not significantly differ from cases found in the review of the literature.

Conclusions: Clinicians practicing in endemic areas should be aware of this rare but serious form of histoplasmosis. The recognition of 5 cases of CNS histoplasmosis in AIDS patients from a single institution suggests that histoplasmosis should be included in the differential diagnosis of the CNS complications of AIDS.

Key Indexing Terms: Histoplasma capsulatum; Histoplasmosis; Central nervous system; HIV; AIDS. **[Am J Med Sci 2016;351(2):177–186.]**

INTRODUCTION

Cases of histoplasmosis occur throughout the world but the most highly endemic region is the Ohio and Mississippi River valley, including East Texas, due to its temperate humid climate.[1] In this region, disseminated histoplasmosis is a frequently seen opportunistic infection in patients with AIDS.[2] Central nervous system (CNS) involvement can be seen in 5-10% of patients with disseminated histoplasmosis.[3] *Histoplasma capsulatum*, however, is usually not a suspected etiologic agent in AIDS patients presenting with CNS disease.[4] We report 5 AIDS patients from our institution that had meningitis, brain lesions and disseminated disease caused by this organism and review additional cases in the literature.

METHODS

Cases of CNS histoplasmosis in patients with AIDS were identified retrospectively by reviewing clinical microbiology and reference laboratory records at the University of Texas Medical Branch in Galveston, Texas between 2004 and 2014. Cases were classified as either proven [positive *Histoplasma* culture from cerebral spinal fluid (CSF)] or probable (positive *Histoplasma* antigen from CSF or positive antigen, culture or histopathological evidence of *Histoplasma* from a non-CNS site in combination with CSF abnormalities consistent with meningeal inflammation and absence of other pathogens). Additionally, a MEDLINE search for cases published in the literature was performed using the keywords: "central nervous system," "CNS," "histoplasmosis," "HIV," "immunocompetent," "immunocompromised" and "transplantation."

RESULTS

We identified 5 cases of CNS histoplasmosis presenting to our institution in the last decade. The clinical characteristics of these patients are summarized in Table 1 (Cases 1-5). These patients were from East Texas, had a mean age of 51 years, and were infected with human immunodeficiency virus (HIV). Out of 5 patients 4 were not on highly active antiretroviral therapy (HAART) at presentation and had uncontrolled HIV RNA viral loads. All patients had CD4 counts of less than 150 cells/μL; whereas counts were very low in 3 cases (6, 7 and 17 cells/μL), they were more preserved in 2 (110 and 148 cells/μL). Involvement of the CNS ranged from primary manifestation of infection to a relapse likely caused by nonadherence to antifungals or HAART, as 3 of these patients had prior history of disseminated histoplasmosis. A total of 4 patients had evidence of non-CNS organ involvement (gastrointestinal tract and lungs) and 1 patient had isolated meningitis and no prior history of disseminated histoplasmosis. Clinical

TABLE 1. Summary of clinical characteristics in AIDS patients with CNS histoplasmosis from a single institution.

Case	1	2	3	4	5
Date of initial diagnosis	08/2004	04/2007	11/2007	05/2008	03/2014
Age (years) sex	49 F	60 M	48 M	48 M	51 M
Absolute CD4 (cells/μl)	110	6	7	17	148
HIV-1 RNA (copies/μl)	<75	>500,000	438,719	22,548	368,000
HAART at presentation	Yes	No	No	No	No
Underlying diagnosis	None	DH in 2006	DH 2001	Colonic histoplasmosis in 2007, disseminated MAC, hepatitis C cirrhosis	Seizure disorder
Non-CNS symptoms (duration)	Abdominal pain and vomiting (2–3 weeks)	Fever, night sweats cough, shortness of breath, abdominal pain, diarrhea and weight loss (2–4 weeks)	Fever, night sweats, cough, abdominal pain, vomiting, diarrhea and weight loss (4–12 weeks)	Fever, chills, shortness of breath, diarrhea and dizziness (2–4 weeks)	Fever (2–4 weeks)
CNS symptoms (duration)	Nuchal rigidity, headache, kerning and brudzinski sign (2–4 weeks)	Nuchal rigidity, headache and photophobia (2-4 weeks)	Nuchal rigidity, headache and visual impairment (4-12 weeks)	Nuchal rigidity, headache, AMS, kernig and brudzinski sign (2–4 weeks)	Nuchal rigidity and seizure (2–4 weeks)
Imaging	Mild ventricular enlargement and brain atrophy (MRI brain)	Miliary opacities (CXR) diffuse enhancing nodules in cerebrum, cerebellum and brain stem (MRI)	Miliary opacities (CXR); small chronic lacunar infarct of right external capsule (CT head)	Diffuse lung nodules, lower lobe opacities, right lung consolidation (CxR)	1 cm ring lesion and basilar enhancement (MRI brain)
CSF analysis	WBC:148, (% P:54, L:30, M:11), RBC: 4, PR: 228, GLU: < 20	WBC: 121, (% P:6, L:84, M:10), RBC:19, PR:101, GLU: 37	WBC: 160 (% P: 0, L: 72, M: 23), RBC: 114, PR: 118, GLU: 34	WBC: 101 (% P: 36, L: 57, M: 5), RBC: 2, PR: 280, GLU: 24	WBC: 415 (% P: 1, L: 89, M: 10), RBC: 1900, PR: 449, GLU: 21
Histoplasma serology	None	CSF CF: < 1:2	CSF ID: positive (1 band)	CSF ID: positive (1 band)	None
Histoplasma antigen	Urine: 15.07[a], serum: negative	Urine: 4.4[a], serum: 63[a]	Urine: negative, serum: negative	Urine: negative, serum: negative, CSF: 4.55[b]	Urine: 3.2[a], serum: negative, CSF: >19[b]
Pathology	None	Endobronchial biopsy, appendix, and small bowel with granulomas and fungus consistent with histoplasma	Endobronchial biopsy with chronic inflammation	Colonic mucosa with granulomas, inflammation, and fungus consistent with histoplasma	None
Culture	No growth	Histoplasma in CSF, BAL, and blood	Histoplasma in CSF and BAL	No growth	Histoplasma in CSF
Antifungal therapy	ABLC 5 mg/kg/d 3 weeks, then ABLC 5 mg/kg/week 3 months, then fluconazole 400 mg orally twice daily (nonadherent)	ABLC 5 mg/kg/d 2 weeks, then itraconazole 200 mg orally twice daily (nonadherent)	ABLC 5 mg/kg/d 6 weeks, then itraconazole 100 mg orally twice daily (initially nonadherent)	ABLC 3 mg/kg/d 6 weeks, then itraconazole 200 mg orally twice daily (nonadherent)	L-AmB 5 mg/kg/d 4 weeks, then itraconazole 100 mg orally twice daily
HAART	Lopinavir, ritonavir, emtricitabine and tenofovir taken before and during diagnosis	None	Lopinavir, ritonavir, emtricitabine and tenofovir started 2 years after diagnosis	None	Darunavir, ritonavir, lamivudine, and abacavir started within 1 m of diagnosis

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