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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TABLE 1. *(continued)*

Case	1	2	3	4	5
Outcome	Nonresolution of infection caused by nonadherence; death in 01/2005 under hospice care	Bowel perforation in 10/2007 with deteriorating course; death in 12/2007	Relapse in 04/2008 because of initial nonadherence; remission	Nonresolution of infection caused by nonadherence; death under hospice care	Remission

ABLC, amphotericin B lipid complex; AMS, altered mental status; ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; CF, complement fixation; CSF, cerebral spinal fluid; CT, computed tomography; CxR, chest radiograph; DH, disseminated histoplasmosis; GLU, glucose (mg/dL); HB, hemoglobin; ID, immunodiffusion; L, lymphocytes; L-AmB, liposomal amphotericin B; M, macrophages; MAC, Mycobacterium avium complex; MRI, magnetic resonance imaging; P, polymorphonuclear leukocytes; PLT, platelet; PR, protein (mg/dL); RBC, red blood cells (cells/μL); WBC, white blood cell (cells/μL).

[a] Enzyme immunoassay (units).

[b] Miravista diagnostics (ng/mL).

presentation was typically severe from neurological impairment requiring hospitalization. Classic signs of meningitis, including headache, nuchal rigidity and Kernig and Brudzinski signs were observed. Altered sensorium, visual changes and seizures were also common. Constitutional, pulmonary and gastrointestinal symptoms were prominent. No patient had oral or cutaneous lesions. Laboratory abnormalities included leukopenia, anemia and abnormal CSF parameters including elevated protein level and hypoglycorrhachia. CSF pleocytosis with lymphocytic predominance was present even in cases with very low-peripheral leukocyte or CD4 counts. Abnormal chest radiographs showed nonspecific patterns including miliary, nodular and lobar infiltrates. Magnetic resonance imaging revealed diffuse nodules or ringed lesions in the brain parenchyma in 2 cases. Diagnosis of histoplasmosis was usually made within 1 week from presentation, however, identification of CNS involvement was more delayed, taking anywhere between 1 and 12 weeks. A total of 3 cases (Cases 2, 3 and 5) had proven infection with positive *Histoplasma capsulatum* cultures in CSF and 2 cases (Cases 1 and 4) had evidence of histoplasmosis by urine and CSF antigens with clinical signs of meningitis. On average, patients received 4 weeks of treatment with a lipid formulation of amphotericin B followed by oral therapy with an azole antifungal, most commonly itraconazole. No surgical interventions were performed. HAART was initiated or continued in 3 cases. Ultimately, 3 patients died with nonresolution of their disease and 2 remained in remission (Table 1).

A sum of 15 cases of CNS histoplasmosis in AIDS were identified in the literature. The clinical characteristics of 13 are summarized in Table 2 (Cases 6-18). Owing to insufficient data, 2 cases were not included. These cases had a mean age of 37 years. Only one was on HAART at presentation. CD4 counts were low, ranging from 3-81 cells/μL. A previous history of disseminated histoplasmosis was found in 9 cases and 7 developed CNS involvement within a year. Nearly all cases had clinical neurologic manifestations and CSF findings revealed pleocytosis, elevated protein level, and hypoglycorrhachia. Brain imaging findings were variable and included no obvious lesions, multiple scattered hyperintensities, diffuse enhancement and space occupying lesions. *Histoplasma* was cultured from CSF in 3 cases (Cases 7, 9 and 17). Treatment consisted primarily of conventional amphotericin B. Out of 9 patients died of their infection.

In addition, 8 cases of CNS histoplasmosis in HIV negative patients were identified. These included 4 immunocompromised (3 solid organ transplantation recipients and one with systemic lupus erythematous) and 4 immunocompetent hosts. Owing to insufficient data, 3 cases were not included. The characteristics available are summarized in Table 3.

TABLE 2. Summary of clinical characteristics in AIDS patients with CNS Histoplasmosis from the literature.

Case	6	7	8	9	10
Date of initial diagnosis	1999	1984	1983	1986	1986
Age (years), sex	29 F	50 M	32 M	42 M	37 M
Absolute CD4 (cells/μl)	66	None	None	None	None
HIV-1 RNA (copies/μl)	<400	None	None	None	None
HAART at presentation	Yes	No	No	No	No
Underlying diagnosis	Bilateral CMV retinitis, pneumonia, DH (1998), pulmonary histoplasmosis (1999)	PCP, kaposi's sarcoma, DH (1983)	Kaposi's sarcoma, DH (1982)	DH (1986)	DH (1985)
Non-CNS Symptoms (duration)	Fever	None	None	None	None
CNS symptoms (duration)	Headache	Disorientation	Agitation	Disorientation	Cranial nerve VII paresis, papilledema
Imaging	None	Scattered small focal lesions (CT head)	No abnormalities (CT head)	None	Right hemispheric enhancing lesion with edema and mass effect (CT head)
CSF analysis	WBC:98, PR: 107.7, GLU: 31	None	None	None	None
Histoplasma serology	None	None	None	None	None
Histoplasma antigen	CSF: 4.6 Serum: 2.1	None	None	None	None
Pathology	None	Brain: histoplasma (postmortem)	Brain: histoplasma (postmortem)	Brain: histoplasma (postmortem)	Brain: histoplasma (postmortem)
Culture	No growth	Histoplasma in Brain and CSF	None	Histoplasma in CSF	
Antifungal therapy	AmB 0.7 mg/kg/d for 3-5 months, then fluconazole 800 mg/d for 2 years	AmB 1 g and L-AmB 2 g	AmB 0.2 g, miconazole 600 mg/d	None	AmB 1.7 g
HAART	Added lamivudine to abacavir and efavirenz	None	None	None	None
Outcome	Remission	Death	Death	Death	Death
Case	11	12	13	14	15
Date of initial diagnosis	None	None	None	None	06/1994
Age (years), sex	43 M	26 M	37 M	41 M	39 M
Absolute CD4 (cells/μl)	3	None	37	None	46
HIV-1 RNA (copies/μl)	>500,000	None	None	None	None
HAART at presentation	No	No	No	No	No
Underlying diagnosis	DH (12 years before presentation), candida esophagitis, cryptosporidium colitis	None	None	Ischemic stroke	None

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Table 2. *(continued)*

Case	6	7	8	9	10
Non-CNS symptoms (duration)	None	Fever and malaise	Fever, weight loss, dyspnea and cough (3 months)	Nausea and vomiting	Fever, anorexia, nausea and productive cough (10 d)
CNS symptoms (duration)	Diplopia 10 d	Right hemiparesis, paresthesia, hyperreflexia, Babinski and chorea	Ataxia, disequilibrium, confusion and personality changes	Headache, blurred vison and diplopia	None
Imaging	Ring enhancing lesion in tegumentum (MRI brain)	Diffuse enhancing lesions surrounded by hyperintensities (MRI brain)	Diffuse hyperintensity lesions basal ganglia (MRI brain) micronodular infiltrates (CXR)	Moderate ventriculomegaly (CT head) Basal ganglia, meninges, subarachnoid basilar cistern and basilar artery enhancement (MRI brain)	Normal (CT head)
CSF analysis	WBC:0, PR: 57, GLU: 88	Reported as normal	WBC:0, PR: 78, GLU: reported as normal	WBC: 62 (% L: 53, M: 38, P:8), RBC:1; PR: 372, GLU: <20	WBC:184 (% M: 95%, P: 5%), RBC:100; PR: 830; GLU: 46
Histoplasma serology	None	None	None	CSF CF: negative intraventricular CSF CF (1:16)	None
Histoplasma antigen	Urine: negative	None	Serum: negative	Urine: negative, Serum: negative, CSF: 4.55	None
Pathology	Brain: histoplasma (postmortem)	Brain: histoplasma	Lung granulomas and yeast like structures consistent with histoplasma	Brain: noncaseating granulomatous inflammation	Cerebral base and spinal cord: granulomas with central necrosis, and histoplasma found inside langerhan cells
Culture	No growth	Histoplasma in brain	Histoplasma in lung	None	No growth
Antifungal therapy	Itraconazole as OI prophylaxis	AmB (50 mg/d) for 30 d, then itraconazole 400 mg/d	Fluconazole 800 mg IV once daily	L-AmB 4 mg/kg IV once daily for 2 weeks, then Itraconazole 400 mg PO once daily for 2 months	AmB

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Table 2. *(continued)*

Case	6	7	8	9	10
HAART	None	Started 6 weeks after diagnosis	None	None	None
Outcome	Nonresolution of infection due to progression of disease; death 5 months after presentation	Remission	Remission	Remission	Death
Case	16	17		18	
Date of initial diagnosis	None	None		10/1988	
Age (years) sex	36 M	36 M		32 F	
Absolute CD4 (cells/μl)	81	6		None	
HIV-1 RNA (copies/μl)	None	None		None	
HAART at presentation	No	No		No	
Underlying diagnosis	Histoplasma PNA (3 years before presentation)	Recurrent oropharyngeal candidiasis, DH (6 months before presentation)		TB (06/1988), DH (12/1987)	
CNS symptoms (duration)	Nuchal rigidity and seizure	Confusion, ataxia, HA and stiff neck		HA, CN neuropathies and mental status changes	
Imaging	No abnormalities (CT head with/without contrast)	Frontal contrast-enhancing lesion with edema and mass effect (MRI and CT)		Meningitis and multiple intraparenchymal lesions (CT head)	
CSF analysis	WBC:64 (% M:95, P:5), RBC:0 PR:119; GLU: 32	WBC: 15; PR:888 ;GLU:14.4		None	
Histoplasma serology	None	None		None	
Histoplasma antigen	None	None		None	
Pathology	Brain: histoplasma (postmortem)	None		Brain: bx negative brain: postmortem: granulomatous meningitis at base of brain; histiocytes containing histoplasma ventricle: histoplasma	
Culture	None	CSF: histoplasma in stain and culture		None	
Antifungal therapy	Fluconazole 100 mg/d	AmB 50 mg/d		AmB	
HAART	None	None		None	
Outcome	Death	Death		Death	

CF, complement fixation; CMV, cytomegalovirus; CN, cranial nerves; CT, computed tomography; CXR, chest radiograph; DH, disseminated histoplasmosis; GLU, glucose (mg/dL); HA, headache; IV, intravenously; L, lymphocytes; L-AmB, liposomal amphotericin B; M, macrophages; MRI, magnetic resonance imaging; P, polymorphonuclear leukocytes; PNA, pneumonia; PR, protein (mg/dL); RBC, red blood cells (cells/μL); WBC, white blood cell (cells/μL); TB, tuberculosis.

TABLE 3. Summary of clinical characteristics in HIV negative patients with CNS histoplasmosis from the literature.

Case	19	20	21	22	23
Date of initial diagnosis	1972	2014	2007	1999	None
Age (years), sex	8 F	62 M	24 F	20 F	73 M
Underlying diagnosis	Renal transplantation, rejection, hepatomegaly	Immunocompetent	Immunocompetent	Immunocompetent	Heart transplantation
Non-CNS symptoms (duration)	None	None	Fatigue (8 months)	None	Weakness and fever (1 week)
CNS symptoms (duration)	Fever, headache, lethargy and seizures (7 d)	Focal seizures	Severe bifrontal headache, disequilibrium, blurred vision and transient paresthesia of the left hand (8 months)	Headache diplopia	Confusion and aphasia (within hours of presentation)
Imaging	No infiltrate (CXR) slow spike, slow flow (EEG)	Multiple lesions, 2 supratentorial ring enhancing lesions (MRI brain)	Large ventricles and increase signal abnormalities in periventricular region (MRI brain)	Enhancing mass in the thalamoencephalic and third ventricular region (MRI brain)	Enhanced punctate foci in parietal and occipital lobes (MRI brain)
CSF analysis	WBC:22, RBC: 2, PR: 110, GLU: 47	None	WBC:5, PR:121, GLU: 10	None	WBC: 36 (% M: 86), PR: 126; GLU: 53
Histoplasma serology	Serum CF: (1:32)	None	CSF CF: 1:8, serum CF: 1:32	None	Serum CF 1:64 (mycelial Ag) 1:16 (yeast Ag) ID: positive
Histoplasma antigen	None	None	Urine: negative	None	Urine: 1.78
Pathology	Meninges: stained with methenamine: budding yeast like elements. spleen: granulomas	Brain: histoplasma brain abscess	None	Meninges: noncaseating granulomas	None
Culture	Meninges and CSF: histoplasma, spleen: no growth	Brain: histoplasma	CSF: no growth	Meninges: histoplasma	Negative

AMS, altered mental status; CF, complement fixation; CXR, chest radiograph; EEG, electroencephalogram; ID, immunodiffusion; GLU, glucose (mg/dL); MRI, magnetic resonance imaging; PR, protein (mg/dL); RBC, red blood cells (cells/μL); WBC, white blood cell (cells/μL).

DISCUSSION

We report 5 cases of CNS histoplasmosis in AIDS. This represents, to our knowledge, the largest case series of this infection from a single institution. In addition, we reviewed 21 additional cases in the literature. Out of 13 of these cases had AIDS, 4 had non-HIV immunosuppression (solid organ transplantation and systemic lupus erythematous) and 4 were immunocompetent hosts.

Clinical Presentation

In this series, AIDS patients in the literature most commonly presented with mental status changes and signs of meningeal inflammation such as headaches and nuchal rigidity, which were also seen in the AIDS cases from our institution. Cranial nerve neuropathies, focal neurological signs and seizures were also common.[3-13] Patients with non-HIV immunosuppression most commonly presented with headache and signs of meningeal inflammation followed by focal neurological signs and mental status changes.[13-16] Infection in immunocompetent hosts presented largely with signs of meningeal inflammation. Mental status changes and focal neurological signs were also prominent, although cranial neuropathies and seizures were less commonly seen.[3,13,17-25] This experience shows that the clinical presentation of CNS histoplasmosis is nonspecific and may mimic other more common etiologies such as cryptococcal or tuberculous meningitis.[4,5] Diagnosis is particularly difficult in cases presenting with isolated CNS involvement and no other clinical or laboratory evidence of disseminated infection. Most patients in this series had low-CD4 counts, however, relatively higher counts (100-150 cells/μL) and undetectable HIV RNA viral loads can be seen, as it occurred in 2 cases.

CSF Findings

Non-HIV immunosuppressed and immunocompetent cases that underwent CSF analysis had pleocytosis, elevated protein and hypoglycorrhachia [13-16,20-24] as did the AIDS cases from our institution. CSF pleocytosis with lymphocytic predominance was seen even in cases with very low-peripheral leukocyte or CD4 counts. In AIDS cases in the literature, however, the most common CSF abnormality was high protein level,[3-9,13] and in one case, CSF parameters were normal.[6]

Neuroimaging Findings

The neuroimaging findings of CNS histoplasmosis are also variable. In AIDS patients, multiple contrast-enhancing intraparenchymal lesions associated with mass effect and edema were seen.[3-6,8-13] Hydrocephalus was found in immunocompetent patients many of whom had ventriculoperitoneal shunts in place at time of diagnosis.[13,17-25] This was likely caused by histoplasmosis. In non-HIV immunosuppressed patients, masses and hydrocephalus were equally prevalent.[13,14]

Diagnostic Testing

Previously reported diagnostic yields of various tests used in the diagnosis of CNS histoplasmosis have ranged as follows: meningeal or brain biopsy, 50–80%; CSF culture, 20–60%; CSF antigen, 40–70%; and CSF antibodies, 60–80%.[26] Only 7 cases in this series had positive serologies (5 CSF and 2 serum). Serologies are of limited value in the initial evaluation because of its lengthy turnaround time and variable sensitivity depending on the level of immunosuppression. Sensitivities of 82% and 85-100% have been previously reported in non-HIV immunosuppressed and immunocompetent individuals, respectively. Conversely, a lower sensitivity of 67-70% has been described in individuals with AIDS. The newer generation antigen assays, allow for a more rapid identification of the fungus, as cultures are insensitive and require prolonged incubation. In individuals with AIDS and disseminated histoplasmosis, antigen detection can provide early diagnosis with a sensitivity of 95%.[26] Clearly, a rapid diagnosis is essential in patients with suspected CNS histoplasmosis. A strongly positive CSF antigen and a negative or weakly positive serum or urine antigen result support primary CNS involvement without overt disseminated involvement (as seen in Case 5), and should not be regarded as result of specimen contamination or passive transport of antigen across the blood brain barrier.[3] This finding suggests that clinicians should not rely solely on serum or urine antigen results when considering the diagnosis of CNS histoplasmosis.

Treatment

Most patients in this series received induction treatment with conventional or a lipid formulation of intravenous amphotericin B (AmB). An initial gradual response (after 3-4 weeks), was seen in the 5 cases treated in our institution. Conversely, of 8 AIDS cases from the literature treated with conventional AmB, 6 died and 2 went into remission. This limited experience suggests that a lipid formulation of AmB may be preferable for the initial treatment in CNS histoplasmosis.[7-8,15,17,18] Other investigators have similarly shown a higher response rate and lower mortality in patients with AIDS and progressive disseminated histoplasmosis treated with a lipid formulation compared with conventional AmB.[27] Selection and optimal dosage of consolidation or "step-down" azole treatment are not well defined for this form of histoplasmosis. A total of 4 cases in our series received oral itraconazole (100-200 mg twice daily) whereas the other received oral fluconazole 400 mg twice daily. Although fluconazole penetrates the CNS better[28] and has been successfully used in induction therapy, it has been shown to be inferior to itraconazole when used for maintenance to prevent relapse.[29] Itraconazole also has been shown to have more antimicrobial activity against *Histoplasma spp*.[28] Optimal itraconazole dosing in patients receiving concomitant ritonavir as part of their HAART regimen is unknown. Cases 3

and 5 in this series had ritonavir as part of their HAART regimen and received itraconazole. Case 3 relapsed because of initial nonadherence but remained in remission when given at least 100 mg twice daily. Case 5 remained in remission with the same dosage. Higher itraconazole doses (200 mg twice or thrice daily) are probably necessary in patients receiving nonprotease inhibitor based-HAART regimens. Although itraconazole levels were not measured in any of these cases, serum levels of itraconazole should be checked early in the course of therapy to ensure adequate drug exposure (concentrations should be at least 1 ug/mL)[3] and to avoid toxicity.[1] Combining AmB with fluconazole or itraconazole has shown no benefit.[28] Newer azole antifungals (posaconazole and voriconazole) demonstrate *in vitro* activity and have been successfully used in a few refractory cases. When other first line options fail or cannot be used, these newer triazoles, particularly posaconazole, may be an alternative.[30,31] There is concern, however, for the development of *in vitro* resistance to voriconazole.[32] Prompt institution of HAART is also essential. There is concern about early initiation of HAART and eliciting immune reconstitution inflammatory syndrome (IRIS) with paradoxical clinical worsening.[33] In this series, however, there were no IRIS cases. In Case 5, early institution of HAART within 1 month after diagnosis did not result in IRIS. This complication is generally considered uncommon in AIDS patients with histoplasmosis, and HAART should be started as soon as possible after initiating antifungal therapy.[1,34] Patients with disseminated histoplasmosis and AIDS that were given HAART had improved responses to antifungals and lower mortality rates than those managed without HAART.[35]

Relapses

Relapses and nonresolution of infection were common in this series and occurred primarily because of lack of adherence to antifungal maintenance therapy and HAART. Therapy with itraconazole should continue for at least 1 year, until CD4 counts are above 150 cells/μL, and cultures as well as *Histoplasma* urine and serum antigens are negative on HAART.[2,7,36] Antifungal therapy was successfully withdrawn in Cases 3 and 5 after immune reconstitution, and these patients remained in remission while continuing HAART. Suppressive therapy should be resumed if patients become nonadherent to HAART or CD4 counts drop below 150 cells/μL. Relapse has been previously shown to be more common in AIDS patients with CNS histoplasmosis compared with those without CNS involvement, but of the CNS cases that relapsed, nonadherence to therapy was the major factor,[2] as was also seen in the current series. Better outcomes, including less relapse and neurologic sequelae, were associated with adherence to HAART and antifungal therapy. Overall, prognosis was poor and nonadherence appeared to be the driving factor for nonresolution of disease and ultimately death in 3 cases from our institution.

CONCLUSION

In conclusion, HIV clinicians practicing in endemic areas should be aware of this uncommon but serious form of histoplasmosis. The recognition of 5 cases of CNS histoplasmosis in patients with AIDS in a single institution suggests that histoplasmosis should be included in the differential diagnosis of the CNS complications of AIDS. Rapid antigen and antibody detection testing of CNS specimens (i.e., CSF) should be submitted when the diagnosis is suspected. If there is clinical suspicion even in the face of negative test results, it is important to continue the search for the diagnosis. Prompt institution of treatment and patient adherence to recommended regimens would result in better outcomes.

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