CASE REPORT

Ring-enhancing Brain Lesions in a Patient with Advanced Human Immunodeficiency Virus from the Central United States of America

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Background: Histoplasmosis is an endemic fungus found worldwide. It most commonly causes pulmonary infections. In patients with defects in cellular immunity it can cause disseminated infections including central nervous system infections.

Case presentation: We present a case of a 44-year-old with advanced human immunodeficiency virus who presented with neurologic complaints. Magnetic resonance imaging of the brain revealed ring-enhancing brain lesions. He underwent brain biopsy of one of the ring-enhancing lesions and histopathology revealed *Histoplasma capsulatum.*

Conclusion: Ring-enhancing brain lesions due to endemic fungi in patients with advanced HIV are uncommon. Nonetheless, this should remain a diagnostic consideration in endemic areas.

Keywords: ring-enhancing brain lesions, human immunodeficiency virus, histoplasmosis, *Histoplasma capsulatum*

BACKGROUND

Histoplasmosis is an infection due to the dimorphic fungi *Histoplasma capsulatum. H. capsulatum* is found worldwide, but is endemic, and particularly prevalent, in the Ohio and Mississippi River Valleys (1).

H. capsulatum is acquired via inhalation of microconidia into the lungs. As a result, the most common form of infection is pulmonary disease. *H. capsulatum* can disseminate and cause infection in any organ. *H. capsulatum* can cause disseminated disease. When it does disseminate it has a predilection for liver and bone marrow. It can also cause disease in the central nervous system. Central nervous system histoplasmosis occurs in 5-10% of those with disseminated histoplasmosis (2). Patients with profound defects in cellular immunity are at increased risk of disease from *H. capsulatum* and disseminated disease.

Opportunistic infections in the setting of human immunodeficiency virus (HIV) have decreased over the past two decades with the introduction of highly active anti-retroviral medications. Despite advances in the care of patients with HIV,

opportunistic infections still occur. Ring-enhancing brain lesions in patients with advanced HIV, usually defined as those with a CD4 cell count less than 200 cells/mm^3, are most commonly due to *Toxoplasmosis gondii*, *Cryptococcus neoformans*, or primary central nervous system lymphoma due to Epstein-Barr virus. In areas where endemic dimorphic fungi are present one must include them in the differential diagnosis of ring-enhancing brain lesions in patients with advanced HIV. The treatment of central nervous system infection due to histoplasmosis in the setting of advanced HIV is a multimodal approach of systemic antifungals and anti-retroviral medications.

CASE PRESENTATION

A 44-year-old Caucasian male from the central United States of America (Missouri) presents with a longstanding history of HIV infection. He was initially diagnosed with HIV in 1991. He has had a history of medication noncompliance with his anti-retroviral therapy. His most recent anti-retroviral therapy consisted of emtricitabine/tenofovir alafenamide fixed dose combination and darunavir/cobicistat fixed dose combination. His most recent labs were a CD4 count of 87 cells/μL and an HIV viral load of 600,000 copies. He has a remote history of neurosyphilis, eleven years prior to presentation, status post treatment with 2 weeks of intravenous penicillin G. RPR at the time of diagnosis of neurosyphilis was 1:8 and following treatment was 1:4. His most recent RPR was 1:16. He also has a history of hepatitis C virus infection without treatment and a history of intravenous drug use with methamphetamines with his last use one month prior to presentation. Approximately 3 weeks prior to presentation he developed right-sided numbness and tingling involving his face and upper extremity, a resting tremor, and new onset stuttering.

He presented to an emergency department for evaluation of his neurologic complaints. Initial laboratory examination revealed: white blood cell 6.5 x 10^3/mcL, neutrophils 63.1%, lymphocytes 28.4%, monocytes 6.7%, eosinophils 1.3%, basophils 0.5%, hemoglobin 12.7 g/dL, platelets 324 x 10^3/mcL, sodium 138 mmol/L, potassium 4.1 mEq/L, chloride 101 mmol/L, CO_2 28 mmol/L, blood urea nitrogen 27 mg/dL, creatinine 1.0 mg/dL, alkaline phosphatase 137 mg/dL, AST 45 U/L, ALT 41 U/L, and bilirubin 0.4 mg/dL. A portable chest x-ray revealed mild left basilar atelectasis. Computed tomography of the chest with contrast revealed scattered tree-in-bud nodules in the lingula and left lower lobe with associated left lower lobe mild bronchiectasis. Computed tomography of his head revealed multiple brain lesions with vasogenic edema. He was admitted and started on penicillin G, sulfadiazine, pyrimethamine and leucovorin. Cerebral spinal fluid (CSF) analysis revealed: white blood cells 2 cells/mcL (segmented neutrophils 6%, lymphocytes 77%, monocytes 16%), red blood cells 179 cells/mcL, protein 57 mg/dL, and glucose 49 mg/dL, CSF VDRL nonreactive, CSF toxoplasma PCR negative and CSF toxoplasma IgG negative and IgM negative. Magnetic resonance imaging of the brain with intravenous contrast was obtained revealed a temporoparietal ring-enhancing lesion with associated vasogenic edema (Figure 1). His symptoms failed to improve after a week and a half of the previously mentioned empiric therapies. He ultimately underwent a left frontal open craniotomy of one of the ring-enhancing lesions and histopathology was obtained (Figure 2). He was diagnosed with central nervous system histoplasmosis. He was started on liposomal amphotericin B 5 milligrams per kilogram

intravenously daily and resumed his previous anti-retroviral medications. He slowly improved over the following weeks.

DISCUSSION

Histoplasmosis is due to the dimorphic fungi *Histoplasma capsulatum* (Figure 2, 3, and 4). *H. capsulatum* is endemic in the Ohio and Mississippi River Valleys (1). It is also endemic in Central and South America. A subspecies, *H. capsulatum var. duboisii*, has also well as been described in parts of sub-Saharan Africa. *H. capsulatum* lives in the soil and is found in higher concentrations in areas with bird droppings and bat guano. *H. capsulatum* is acquired via inhalation of microconidia into the lungs. As a result, the most common form of infection is pulmonary disease. *H. capsulatum* can disseminate, and commonly does so without symptoms, and can cause infection in any organ. When *H. capsulatum* does disseminate it has a predilection for the liver and bone marrow.

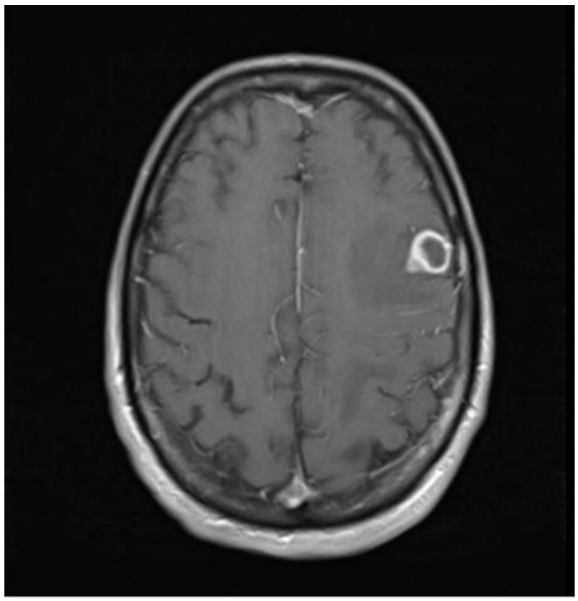

Figure 1. Brain MRI T-1 weighted post-contrast

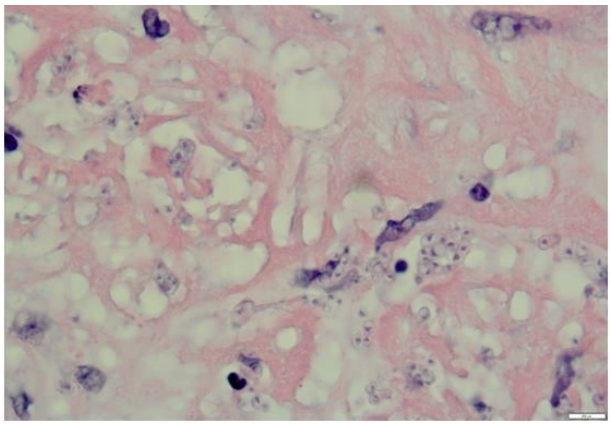

Figure 3. Brain biopsy hematoxylin and eosin stain, high magnification 100X, oil immersion

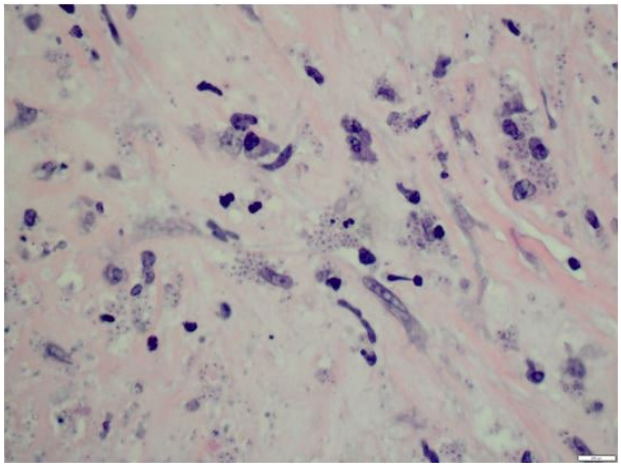

Figure 2. Brain biopsy hematoxylin and eosin stain, low magnification 600X

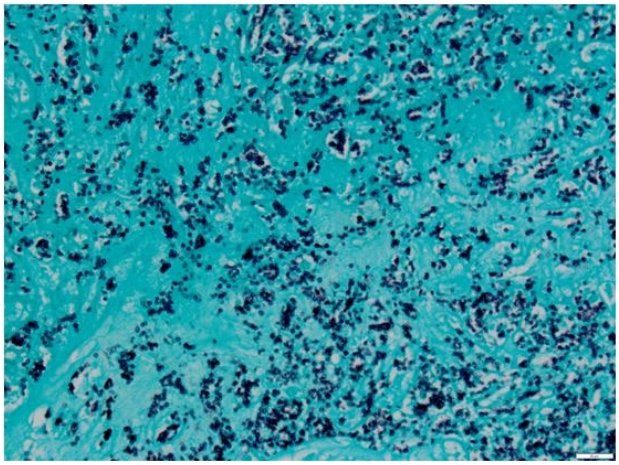

Figure 4. Brain biopsy Gomori Methenamine-Silver (GMS) Nitrate Stain

Patients with profound defects in cellular immunity are at increased risk of disease from *H. capsulatum*. This includes patients with advanced HIV, those receiving anti-TNF alpha inhibitors, and chronic high dose corticosteroid use. Among patients with advanced HIV, those with CD4 cell count less than 150 cells/μL are at the highest risk for infection (2,3). In a recent series of 303 patients with HIV infection who had invasive fungal infections (IFI), histoplasmosis represented 9.1% of IFI (4). In that same series, for patients with histoplasmosis, the median CD4 cell count was 13 cells/μL and all patients had a CD4 count less than 50 μL (4). Disseminated histoplasmosis, that is histoplasmosis at a site other than or in addition to lungs or cervical or hilar lymph nodes, was included in the revision of the Center for Disease Control Surveillance Case Definition for Acquired Immunodeficiency Syndrome in 1987 (5).

Ring-enhancing brain lesions in patients with advanced HIV, usually define as those with a CD4 cell count less than 200 cells/mm^3, are most commonly due to *Toxoplasmosis gondii*, *Cryptococcus neoformans*, or primary central nervous system lymphoma due to Epstein-Barr virus. In areas where endemic dimorphic fungi are present one must include them in the differential diagnosis of ring-enhancing brain lesions in patients with advanced HIV. Endemic dimorphic fungi that have been documented to cause ring-enhancing brain lesions in patients with advanced HIV include *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, and *H. capsulatum* as in this case (6). In immunocompromised patients with ring-enhancing brain lesion, a travel history with exploration into possible high-risk exposures should be elicited. High risk exposures would include activities that resulted in soil disruption and aerosolization of fungal spores in endemic areas. Additionally, spelunking has been associated with histoplasmosis due to the disruption of bat guano.

Central nervous system infections due to histoplasmosis occur in 5-10% of those with disseminated histoplasmosis (2). Central nervous system infection due to histoplasmosis can present as meningitis or as focal parenchymal lesions in the brain and brain stem. Focal parenchymal lesions are referred to as histoplasmomas. These lesions present radiographically as masses or ring-enhancing brain lesions often with associated vasogenic edema and mass effect. Symptoms of CNS histoplasmosis include fever, headache, alterations in mental status, seizure, and focal neurologic deficits.

The diagnosis of histoplasmosis is confirmed by isolation of the fungus in blood, cerebral spinal fluid, expectorated sputum or bronchoscopically obtained pulmonary specimens, or tissue culture (including bone marrow biopsy). Another confirmatory diagnostic modality is histopathology which can reveal the characteristic budding yeast forms on permanent sections of tissue. Indirect diagnostic modalities include serum and urine histoplasma antigen and serum antibody detection.

Treatment of central nervous system infection due to histoplasmosis is a multimodal approach of systemic antifungals and anti-retroviral medications. Systemic antifungal medications used for central nervous system infection due to histoplasmosis are divided into induction therapy and maintenance therapy. Induction therapy is achieved with liposomal amphotericin B dosed at 5 milligrams per kilogram intravenously daily for a duration of 4 to 6 weeks (7). Maintenance therapy is continued with itraconazole 200 milligrams orally twice daily for at least 12 months (7). Long term suppressive therapy, or secondary

prophylaxis, is commonly required for patients who remain immunocompromised. The duration of secondary prophylaxis is determined by reconstitution of the immune system on anti-retroviral therapy and lack of evidence of ongoing infection with *H. capsulatum* (8). Criteria for discontinuing secondary prophylaxis include having received a triazole treatment for >1 year, *and* negative fungal blood cultures, *and s*erum Histoplasma antigen <2 ng/mL, *and* CD4 count >150 cells/mm3 for ≥6 months in response to anti-retroviral therapy (8).

HIV associated opportunistic infections, including invasive fungal infections, have declined since the introduction and increased use of highly active anti-retroviral therapy (9, 10). Invasive fungal infections due to endemic fungi are a rare but important cause of morbidity and mortality in patients with advanced HIV infection. When caring for patients with advanced HIV infection, one should keep in mind the geographic exposures of these patients to endemic fungi.

Notes

Potential conflicts of interest: D.S. serves on the speakers' bureau for Sanofi Pasteur Vaccines. K.S. no conflicts

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