Case in Point

Disseminated Histoplasmosis to the Brain

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An immunocompetent patient living in an endemic area presented with headache, weakness, gait instability, and weight loss. Brain imaging showed enhancing lesions, but fungal infection was not initially suspected. This author reminds clinicians to keep histoplasmosis in the differential diagnosis when enhancing lesions are identified.

Histoplasmosis is the most prevalent endemic mycosis in the United States.[1] *Histoplasma capsulatum*, the causative microorganism of the disease, is a fungus that remains in a mycelial form at ambient temperatures but converts to a yeast at body temperature.[2] The fungus is found in the soil, especially near areas contaminated by bird and bat droppings.[3] Contaminated soil can have infectious effects for years.[2]

Most *H. capsulatum* infections are self-limiting; susceptibility to severe infection is increased markedly with impaired cellular host defenses.[2] In adults who are immunocompetent, disseminated disease is rare.[2] This article details the case of one such patient—a man with histoplasmosis disseminated to the brain.

INITIAL EXAM

A 68-year-old man presented to the emergency department (ED) of a medical facility located in Kansas with headache and generalized weakness. He reported experiencing balance problems and a 20-lb weight loss over the past two months. By the time he presented to the ED, his gait instability had worsened to the point that he was wheelchair bound.

He reported having the headache and weakness consistently for the past month. The headache was persistent although worse in the morning. It was diffuse and throbbing, and it awakened him from sleep at night. He had no documented fever and reported no history of nausea, vomiting, cough, hemoptysis, or seizures. The patient was HIV negative and reported no alcohol or intravenous drug abuse, but he did smoke two packs of cigarettes a day for the past 40 years. His past travel was limited to one trip to Mexico 16 years earlier.

His past medical history was significant for obstructive sleep apnea, atrial fibrillation, and excision of a sebaceous cyst at the right shoulder (in July 2003), which had been complicated by abscess formation and osteomyelitis of the right acromioclavicular joint. The abscess had been drained, and a pus culture showed *Pseudomonas aeruginosa* and *Enterobacter cloacea*—both of which were sensitive to cefepime and levofloxacin. The patient received a six-week course of intravenous antibiotics.

Physical examination showed stable vital signs and no jugular venous distension, carotid bruits, or enlargement of the cervical or supraclavicular lymph nodes. Examinations of his chest, heart, abdomen, and musculoskeletal system yielded normal results.

Neurologic examination revealed an alert man who was oriented to time, place, and person. His Mini-Mental State Examination score was 24, indicating some cognitive impairment.[4] His gait was unstable with tendency to fall on the right side. Vibration and pinprick sensation were normal on the left side of his body but impaired on the right side. He exhibited no cerebellar signs and his position sense and light touch were intact.

Results of laboratory testing included a white blood cell count of 3,600 cells/μL (reference range, 4,500 to 11,000 cells/μL) with neutrophils 53.6%, lymphocytes 32.9%, monocytes 11.3%, eosinophils 1.9%, and basophils 0.3%; a hemoglobin level of 13.1 g/dL (reference range, 14 to 17.5 g/dL); and a platelet count of 121 x 10^3 cells/μL (reference range, 150 to 350 x 10^3 cells/μL). His lac-

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tate dehydrogenase level was 253 U/L (reference range, 100 to 200 U/L) and his thyroid stimulating hormone level was 2.96 mIU/L. Results of the patient's basic metabolic panel and liver function tests were normal. His international normalized ratio was therapeutic at 2.39. Urine testing for histoplasma Ag was negative.

A computed tomography (CT) scan of the patient's brain was performed. It showed numerous ring enhancing lesions in both cerebral hemispheres with associated vasogenic edema (Figure 1). The lesions were thought to be metastatic brain tumors and the patient was admitted to the hospital for treatment and further testing.

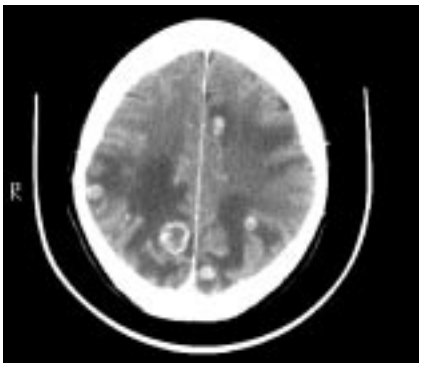

Figure 1. Computed tomography scan of the patient's brain, showing numerous ring enhancing lesions in the cerebral hemispheres bilaterally in the cortical and subcortical regions with associated vasogenic edema. The largest ring enhancing lesion in the right occipital lobe measures 1.7 x 1.6 cm in dimension. No midline shift is identified.

HOSPITAL COURSE

We initiated treatment with a loading dose of dexamethasone 10 mg IV, with subsequent doses of 4 mg IV every six hours. A CT of the chest, abdomen, and pelvis showed bilateral adrenal enlargement but was otherwise normal. Colonoscopy, performed in order to rule out colorectal cancer, revealed only diverticulosis. Purified protein derivative test results were negative, and a lumbar puncture yielded normal results. An erythrocyte sedimentation test revealed a rate of 28 mm/hr. A stereotactic brain biopsy was performed, and the results showed intracellular and extracellular fungi consistent with *H. capsulatum* (Figure 2).

Based on the brain biopsy findings, more testing was conducted to identify an underlying cause and determine the extent of the fungal infection. The patient's CD4 T-lymphocyte count was low at 310 cells/µL (reference range, 490 to 1,740 cells/µL). Test results for various infections—including hepatitis B and C viruses, human herpesvirus-6, cytomegalovirus, respiratory syncytial virus, measles virus, parainfluenza virus, enterovirus, adenovirus, parvovirus B19, coronavirus, mycoplasma, rickettsia, and Borrelia burgdorferi—were negative. Bone marrow biopsy, a 24-hour urine collection for protein electrophoresis, and skeletal survey all yielded normal results.

Antifungal treatment was initiated, with conventional amphotericin B 0.7 mg/kg/day IV infusion. After a total of five days, treatment was switched to itraconazole. The dexamethasone dose was tapered, but the patient's blood pressure (BP) measurements were low. His serum cortisol level also was low at 4.5 µg/dL (reference range, 5 to 25 µg/dL). Therefore, treatment with prednisone twice per day (5 mg in the morning and 2.5 mg in the evening) and fludrocortisone 0.1 mg once per day was initiated. His BP returned to normal over the next 48 hours.

The patient was discharged home 21 days after admission. His medications included prednisone twice per day, fludrocortisone once per day, and itraconazole 200 mg capsules twice per day. Three months later, his CD4 T-lymphocyte count had improved to 424 cells/µL. Repeat brain imaging was performed at six-month follow-up and showed a slight decrease in the size of the brain lesions. Fludrocortisone treatment was stopped at that time, and the patient's BP remained normal while he was taking prednisone alone. A decision was made to continue the itraconazole and steroid therapy and evaluate him every six months with a brain imaging study. After two years, the patient's CD4 T-lymphocyte count improved to 860 cells/µL. He was fine for four years after his initial presentation. He then was diagnosed with lung cancer and subsequently died one month prior to publication of this case report.

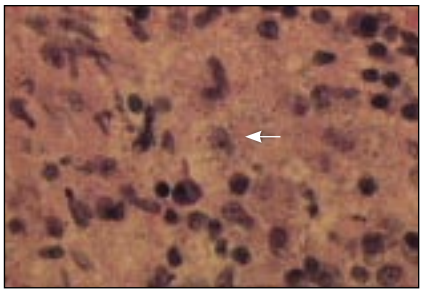

Figure 2. The patient's brain biopsy with hematoxylin and eosin stain, showing intracellular and extracellular fungi consistent with *Histoplasma capsulatum*. A histiocyte with intracellular fungi is identified (arrow).

ABOUT THE CONDITION

Every year, histoplasmosis infects about 250,000 people in the United States. Most infections occur in the Ohio and Mississippi River valleys, along the so-called "Histo Belt."[3,5] The region includes many Midwestern states, including all of Arkansas, Kentucky, Missouri, Tennessee, and West Virginia, as well as large portions of Alabama, Illinois, Indiana, Iowa, Kansas, Louisiana, Maryland, Mississippi, Nebraska, Ohio, Okla-

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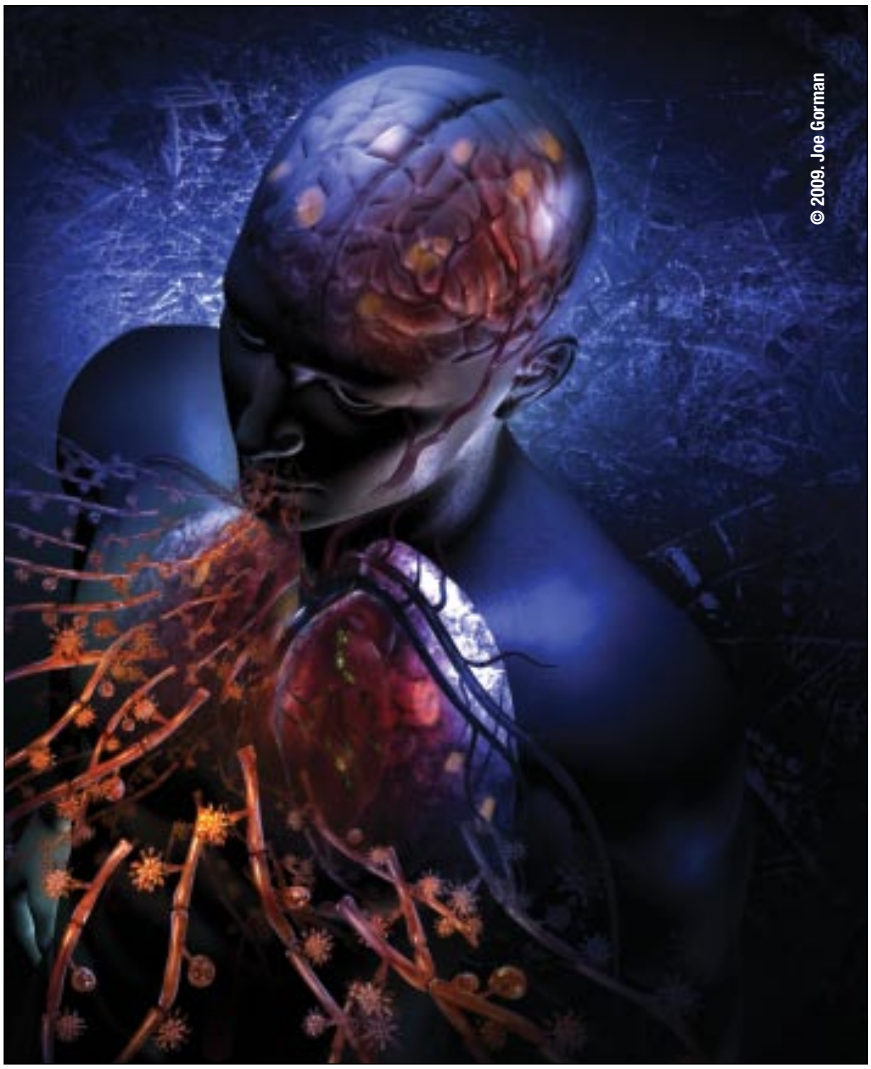
homa, Texas, and Virginia.[5] People living in these regions—where up to 90% of the adult population has been infected with histoplasmosis[5]—might be exposed to histoplasmosis-contaminated soil through many day-to-day activities, including being in close proximity to a construction site.[3]

Overall, surveillance for histoplasmosis has been passive, depending on voluntary reporting by health care providers. Unless an outbreak occurs, individual cases are required to be reported in only 13 states (Alabama, Arkansas, Delaware, Illinois, Indiana, Kentucky, Michigan, Minnesota, New York, Ohio, Pennsylvania, Rhode Island, and Wisconsin).[1] Several outbreaks have occurred, including in Mason City, IA in 1962 and 1964 and in Indianapolis, IN between 1978 and 1979 and in 1980.[1]

Varying degrees of infection

Most *H. capsulatum* infections are self-limiting. Once histoplasma microconidia are inhaled into the lungs, they germinate into yeasts, and neutrophils, monocytes, lymphocytes, and natural killer cells are attracted. Macrophages assist in spreading the organism through the lymphatic system and the blood to adjacent lymph nodes, adrenal glands, bone marrow, and wandering histiocytes. Organisms are confined to macrophages and rarely are seen growing freely within the tissue spaces. In disseminated infection, however, the organisms occasionally can be seen in peripheral blood monocytes.[6]

Because of this self-limiting nature of histoplasmosis, most people who have been exposed to *H. capsulatum* do not experience any signs or symptoms. In fact, they may never know they have been infected. If signs of acute pulmonary histoplasmosis do occur, they include fever, malaise, headache, and weakness.[3] People



with underlying lung disease may develop chronic pulmonary histoplasmosis—at a rate of 100,000 persons per year in endemic areas.[2]

People who have compromised immune systems may develop disseminated histoplasmosis—at a rate of 1 per 2,000 cases of histoplasmosis.[2] People with conditions that impair the ability to defend against intracellular pathogens, such as AIDS; take medications that are immunosuppressive, such as steroids, methotrexate, and anti–tumor necrosis factor drugs; are older or very young; have idiopathic CD4 lymphopenia; or have had organ transplantation are at heightened risk for progressive disseminated histoplasmosis.[6] Symptoms of disseminated disease have been reported as including fever, malaise, anorexia, and weight loss.[3] Whether or not treatment is administered, up to 10% of patients develop adrenal insufficiency.[2] Interestingly, a person may be infected with *H. capsulatum* and, years later, develop an immunosuppressive condition that allows the infection, which was controlled until that point, to reactivate.[3] Therefore, patients may present shortly after exposure or years later and may ex-

perience asymptomatic periods interrupted by symptomatic relapses.

H. capsulatum can infect the central nervous system (CNS) as an isolated infection or as a result of disseminated disease.[3] If this occurs, the infection frequently is fatal or discovered only upon autopsy.[7] Although CNS involvement usually occurs in patients who are immunocompromised, a review of 11 cases of isolated histoplasmosis of the CNS in immunocompetent patients was published in 2006 by Schestatsky and colleagues.[8] They reported the presenting symptoms as including headache, meningeal irritation signs, and mental status changes. Almost all patients had signs of ventricular dilatation. Hydrocephalus also was identified as an important manifestation. Diagnosis involved immunodiffusion analysis of the cerebrospinal fluid. The authors suggested that immunocompetent patients with chronic lymphocytic meningitis be tested for CNS histoplasmosis, especially those patients who live in an endemic area, work in construction areas, or are hospitalized while construction is ongoing in the hospital.[8]

The patient in this case report did have CNS manifestations, but he exhibited no signs of meningitis and had normal CSF findings. He also exhibited hypotension and had a positive cosyntropin stimulation test, suggestive of adrenal insufficiency. Therefore, the patient was believed to have had disseminated histoplasmosis with secondary adrenal insufficiency (although an adrenal biopsy was not performed). If this patient had no hypotension and did not require steroids, his diagnosis would have been isolated CNS histoplasmosis.

At first, the suspected cause of the patient's disseminated histoplasmosis was believed to be idiopathic CD4 lymphopenia. This condition is diagnosed by a documented absolute CD4 T-lymphocyte count of less than 300 cells/μL (or of less than 20% of total T-lymphocyte cells on more than one occasion), no evidence of HIV infection, and absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T-lymphocyte cells.[9] Kortsik and colleagues documented the first case of pleural effusion due to *H. capsulatum* infection in a patient with idiopathic CD4 lymphocytopenia. Laboratory tests revealed lymphocytopenia with low CD4 T-lymphocyte cells (less than 100 cells/μL) and a decreased CD4 T-lymphocyte/CD8 T-lymphocyte ratio. HIV serology was repeatedly negative. The patient was treated with itraconazole and the pleural effusion resolved.[10]

Once antifungal treatment was administered in our patient, his CD4 T-lymphocyte count began to rise, and continued to rise with subsequent follow-up. This makes a diagnosis of CD4 lymphopenia unlikely. Rhew and colleagues did report reversible CD4 T-lymphocyte depletion in a patient who had disseminated histoplasmosis and who was HIV negative.[11] Our patient was HIV negative, with no specific immunodeficiency identified that would explain the disseminated histoplasmosis.

Diagnosing disseminated disease

Disseminated histoplasmosis with neurologic location is misleading, mimicking tuberculosis or cancer. Arai and colleagues reported the case of a 44-year-old man who presented with headache but had no evidence of systemic infection. Malignant lymphoma was suspected after magnetic resonance imaging of the brain showed enhancing masses. Autopsy showed the patient died of histoplasmosis, which had been disseminating rapidly.[7]

The differential diagnosis of numerous ring enhancing lesions in the cerebral hemispheres includes metastatic brain tumors from lung cancer, breast cancer, melanoma, colorectal cancer, and renal cell cancers[12]; primary intracranial tumors, such as anaplastic astrocytomas; primary CNS lymphomas; abscesses; fungal infections; granulomas, such as tuberculosis; parasitic infections, such as cysticercosis and toxoplasmosis; solitary, large plaques of multiple sclerosis; and vascular malformations.

In order to obtain formal mycologic evidence, biopsy is needed. Biopsy samples can be evaluated for *H. capsulatum*'s yeast phase in tissue or in circulating blood phagocytes. Another option for diagnosis is Histoplasma antigen detection, which is being used increasingly in immunosuppressed patients (mostly with AIDS). Other fungal infections (namely blastomycosis and aspergillosis) can be implicated by false positives, however. Polymerase chain reaction techniques are not useful in diagnosis as of yet. Serology testing is not helpful in establishing a diagnosis in immunocompromised patients because Histoplasma antigen often is not detected.[13] In fact, this testing is not very useful in immunocompetent patients either because elevated antibody titers persist for years following initial infection.[14]

Treatment

Mortality for disseminated histoplasmosis without treatment is 80%,[15] but it can be reduced to less than 25% with antifungal therapy.[16] Prognosis can be affected according to inoculum, immunodeficiency, age of the patient, and diagnosis delay.[17] When prescribing antifungal agents, providers must keep adverse drug interactions in mind.

The antifungal agents most important in the treatment of histoplasmosis are amphotoricin B and itraconazole. Although fluconazole plays an integral role in treatment of fungal meningitis, its role in the treatment of histoplasmosis is hampered by reduced activity and potential development of resistance. Nevertheless, there is one case that showed dramatic improvement of disseminated histoplasmosis with CNS involvement in an HIV-infected patient upon induction of therapy with fluconazole.[18] A murine model of CNS histoplasmosis, however, showed that a combination of amphotericin B and fluconazole was not superior to amphotericin B monotherapy.[19]

In cases surveyed from the 1950s and 1960s by The National Communicable Disease Center Cooperative Mycoses Study Group, amphotericin B was found to induce a response in over 70% of patients.[2,20] The agent reduced the mortality rate from 83% in historical controls to 23% in treated patients.[20] The clinical response to amphotericin B treatment often is dramatic.[21] Improvement in fever is the earliest evidence for response, occurring within one week in over 80% of patients.[22] Weight gain and resolution of fatigue follow in two to four weeks.[23]

Unfortunately, relapse can occur in 10% to 20% of patients with disseminated histoplasmosis treated with amphotericin B.[21] Underlying immunosuppression,[21] adrenal insufficiency,[24] and total courses of less than 35 mg/kg of amphotericin B may increase the likelihood of relapse.[25]

Amphotericin B remains the treatment of choice for patients with moderately severe or severe clinical manifestations of histoplasmosis. Since liposomal preparations achieve higher concentrations in the spleen and liver than the standard preparations, the liposomal preparations of amphotericin B may be preferred in patients with preexisting renal disease or those who experience severe adverse effects of conventional amphotericin B.[26] Because the liposomal form is not available at our facility, the patient in this case was treated with conventional amphotericin B.

An overall dose of amphotericin B 50 mg/day should be administered to patients weighing more than 50 kg, and a dose of 1 mg/kg/day should be administered to patients weighing less than 50 kg.[26] Itraconazole is an effective treatment for 85% to 100% of patients with mild or moderately severe manifestations of disseminated histoplasmosis[23]; therefore, amphotericin B treatment could be switched to itraconazole within three to seven days in most patients (or within seven to 14 days for severely ill patients).[26]

All clinical and laboratory findings, including the erythrocyte sedimentation rate and histoplasma antigen levels, should resolve before treatment is discontinued. For disseminated histoplasmosis, itraconazole should be given for a minimum of 12 months; chronic pulmonary histoplasmosis may require longer courses. If amphotericin B is used as the only treatment for disseminated histoplasmosis or chronic pulmonary histoplasmosis, the total dosage of amphotericin B should be at least 35 mg/kg, given over two to four months. Patients with AIDS and patients and who relapse after adequate courses of amphotericin B or itraconazole require daily chronic, suppressive treatment with itraconazole 200 mg. Patients who cannot tolerate itraconazole can be treated with weekly or biweekly amphotericin B (50 to 100 mg) and fluconazole 400 mg daily. Poor tolerability of the amphotericin B and lower efficacy of the fluconazole are notable limitations of both of these alternatives.[26]

IN CONCLUSION

Clinicians should maintain a high index of suspicion of disseminated histoplasmosis in patients presenting with enhancing lesions in their imaging studies in endemic areas. Immunocompetency does not exclude disseminated histoplasmosis from the differential diagnosis. ●

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