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Case Report

Isolated central nervous system histoplasmosis in an immunocompetent patient: 53-month hiatus to diagnosis and treatment

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Chronic meningitis may result from a wide range of etiologies, both infectious and noninfectious, and is often diagnostically challenging. In most series, tuberculosis remains the most common recognized cause. Of the fungal diseases resulting in chronic meningitis, *Cryptococcus* is the most common. When untreated, the infectious meningitides typically exhibit an inexorably progressive course with high morbidity and mortality. We report a patient with chronic meningitis due to *Histoplasma capsulatum* who exhibited a remarkably benign course despite being untreated for the disorder for more than 4 years. *Journal of NeuroVirology* (2010) **16,** 472–474.

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Introduction

Chronic meningitis, typically a subacute and insidious process, is often diagnostic enigma. The potential diagnostic spectrum for chronic meningitis is broad and includes infectious diseases, inflammatory and vasculitic disorders, neoplasms, and toxic exposures (Ellner and Bennett, 1976; Cohen 2005). Frequently, the etiology remains uncertain and treatment is undertaken empirically. In a retrospective survey of chronic meningitis from New Zealand between 1967 and 1983, the etiology could be identified in only 55 (66%) of 89 patients (Anderson and Willoughby, 1987). Tuberculosis was the most common recognized underlying etiology, followed by carcinoma and *Cryptococcus neoformans* (Anderson and Willoughby, 1987). Although it has been suggested that this etiological distribution is fairly representative of most European countries, the epidemiology of chronic meningitis varies significantly with geographic distribution (Hildebrand and Aoun, 2003).

One of the rare etiologies of chronic meningitis is histoplasmosis. Histoplasmosis is endemic in the Ohio, Missouri, and Mississippi river valleys (Ajello, 1971) and is also observed in South American countries (Rivera *et al*, 1992). In these endemic areas, infection with *Histoplasma capsulatum* is common, but most infections are clinically silent and resolve without complication (Goodwin *et al*, 1980; Wheat *et al*, 2000). Central nervous system (CNS) involvement generally occurs in immunosuppressed individuals or those with disseminated disease, a rare condition with an estimated case rate of 1 per 100,000 to 500,000 infected people per year (Goodwin *et al*, 1980). Despite disseminated infection, the CNS if involved in only 5% to 24% of patients (Salaki *et al*, 1984; Wheat *et al*, 1990) and only one quarter of these patients exhibit neurological symptoms (Wheat *et al*, 1990).

We report a young adult woman with a $4^1/_2$-year history of undiagnosed isolated histoplasma meningitis who made an excellent recovery following antifungal treatment.

Case report

This 24-year-old white female, a horse trainer, developed headaches that were ascribed to sinusitis and treated with antibiotics in April 2004. Soon after, she

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Table 1 Blood levels (μg/ml) and dosing of itraconazole (capsules taken with food and soda)

Date (month/day/year)	Itraconazole	Hydroxyitraconazole	Dosing (200 mg dose)
10/30/08	.3	.5	Begins as TID 10/23/10
11/6/08	.4	.9	TID
11/11/08	1.4	2.2	TID
1/15/09	2.1	4.2	TID
3/24/09	4.4	7.8	TID
5/8/09	5.9	9.8	TID
8/20/09	4.7	8.2	TID
10/21/09	1.0	1.8	BID (since 8/20/10 because of hypertension and low testosterone)
3/11/10	1.5	2.2	BID (scheduled to end 10/23/10)

Note. Expected blood levels (μg/ml) after 36 days of oral 200 mg dosing are 2.0 ± 1.4 for itraconazole and 2.6 ± 1.7 for hydroxyitraconazole (bioactive metabolite).

reported horizontal diplopia and was found to have a right sixth nerve palsy and bilateral papilledema. On examination, she was afebrile, exhibited no neck stiffness, and was otherwise neurologically normal. A magnetic resonance imaging (MRI) of the head with and without contrast was normal. Cerebrospinal (CSF) revealed an opening pressure of 50 mm. The CSF had 112 white blood cells/ml (WBCs; 100% lymphocytes), glucose 17 mg/dl with blood glucose of 90 mg/dl, and proteins 66 mg/dl. The CSF immunoglobulin G (IgG) was elevated at 9.5 mg/dl, albumin index was elevated at 10.3, IgG synthesis rate was 27.3 mg, and IgG index 1.19. She had positive oligoclonal bands and a normal myelin basic protein. CSF Venereal Disease Research Laboratory test (VDRL), cryptococcal antigen, and bacterial, fungal, and viral cultures were negative. Human immunodeficiency virus (HIV) serology, Lyme titers, angiotensin-converting enzyme levels, erythrocyte sedimentation rate (ESR), C-reactive protein, and urinary histoplasmosis antigen were negative or normal. She was discharged with a diagnosis of probable viral meningitis and noted resolution of the headaches and diplopia while on acetaminophen.

In April 2007, she moved to South Africa where she continued to work in the horse industry. In April 2008, she moved to Florida and began to notice excessive fatigue, frequent and severe bifrontal headaches, a sense of imbalance, blurred vision, and transient paresthesiaes of the left hand. On August 7, 2008, examination showed papilledema, but was otherwise normal. An MRI of the brain revealed large ventricles and increased signal abnormalities in the periventricular region. Intracranial MR angiography and venography (MRA and MRV) were negative. A battery of laboratory work, including complete blood cell count (CBC), ESR, comprehensive metabolic panel, hemoglobin A1c, antinuclear antibody (ANA), rheumatoid factor, thyroid function studies, B12, rapid plasma reagin (RPR), Lyme antibody, and coagulation studies, was normal. Serum IgG showed a polyclonal gammopathy with both kappa and lambda light chains. Lumbar puncture showed an opening pressure of 25 mm. CSF WBCs were 5, glucose 10 mg/dl, and protein 121 mg/dl. Measures of CSF IgG were elevated, with CSF IgG 21.3, IgG index 1.14, and IgG synthesis 69.4. There were three oligoclonal bands. Cytology and cultures for bacteria and fungi were negative. On acetaminophen 250 mg daily, she noted an improvement in her thinking, fatigue, and resolution of her headache.

On September 3, 2008, she presented for a second opinion. General physical examination was normal. She was alert and fully oriented, but had a difficult time relating her history in a coherent fashion. She failed to perform 3-step serial commands completely as well as simple calculations. There was mild bilateral papilledema. Laboratory tests excluded infections due to HIV, cytomegalovirus, syphilis, herpes simplex virus, trypanosomiasis, blastomycosis, cryptococcosis, coccidioidomycosis, cysticercosis, *Mycobacterium*, and schistosomiasis.

A cranial MRI showed interval enlargement of the ventricles, but no meningeal enhancement. Chest x-ray and computed tomography (CT) scans of chest, abdomen, and pelvis were normal. Lumbar puncture (LP) was repeated with an opening pressure of 21 mm. CSF WBCs were 38 (25 lymphocytes and 7 monocytes), protein 132 mg/dl, and glucose 13, with serum glucose of 100 mg/dl. CSF complement titers for *Histoplasma capsulatum* yeast was 1:8 and for mycelia 1:1, whereas blood titers for both were 1:32. No histoplasma antigen was detected in the urine.

She was initially started on acetazolamide and AmBisome 300 mg daily for 5 weeks intravenously and then continued on itraconazole capsules (see Table 1). She was seen periodically thereafter with serial LPs to assess disease resolution. She reported rare, mild headaches thereafter, but was otherwise asymptomatic. On July 24, 2010, a repeat LP showed an opening pressure of 12 mm, 0 WBCs, protein 42 mg/dl, glucose 51 mg/dl, with peripheral of 92 mg/dl. The IgG index was elevated at 0.79, but other parameters were negative. Oligoclonal bands remained positive. Acetazolamide was discontinued

August 2, 2010, and itraconazole was reduced due to newly found hypertension and low total blood testosterone.

Discussion

Our patient had neither features of immunosuppression nor disseminated histoplasmosis. Despite the inability to culture *Histoplasma* from our patient's CSF or other body fluids, she fulfilled diagnostic criteria for the illness, including a compatible clinical illness of at least 3 weeks duration, laboratory evidence of the disease (CF titers for yeast and mycelia in the blood), and both clinical and laboratory evidence of CNS involvement (CF titers for yeast and mycelia in the CSF) (Schestatsky *et al*, 2006). Therefore, she had isolated CNS histoplasmosis. Diagnosis of the offending microorganism is particularly difficult in this context, unlike disseminated histoplasmosis in which bone marrow and blood cultures are positive in 50% (Wheat, 2001) and for which imaging studies, such as chest computerized axial tomography, may reveal evidence of granulomatous disease that can be biopsied.

The most common presentations of CNS histoplasmosis include (1) chronic meningitis; (2) symptomatic mass lesions (histoplasmomas); and (3) symptomatic cerebral emboli from *H. capsulatum* endocarditis (Livas *et al*, 1995; Schestatsky *et al*, 2006). In patients with chronic meningitis, delays in diagnosis from symptom onset of 2 to 6 or more months are not unusual (Schestatsky *et al*, 2006). Although delayed therapy of infectious meningitides is generally fatal, rare individuals have been reported with extensive delays to the correct diagnosis of histoplasmosis CNS disease. Rivera and colleagues described a female first diagnosed at age 18 whose neurological presentation of ataxia and communicating hydrocephalus dated to $8^1/_2$ years earlier (Rivera *et al*, 1992). Repeated CSF fungal cultures were negative until age 18 when the organism was grown from CSF and biopsy of occipital bone and bone marrow, but not brain, revealed granulomas and rare yeasts (Rivera *et al*, 1992). Because of the fastidious nature of *H. capsulatum*, complementary studies that rely on the immune response to the microorganism may be required for diagnosis.

Our patient illustrates the difficulty in diagnosing histoplasma meningitis. She also demonstrates that a lengthy delay to time of diagnosis does not always portend a poor prognosis. This finding is consistent with the observation that individuals with chronic idiopathic meningitis typically, although not invariably, have a benign course despite a prolonged illness (Smith and Aksamit, 1994). Clinicians must have a high index of suspicion for histoplasmosis in a patient with chronic meningitis living in an endemic area.

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