MiraVista DIAGNOSTICS
Rapid Fungal Testing. Accurate Results.

Noninvasive Diagnosis of Central Nervous System Blastomycosis

By Heather Wheat-Largura, DDS | *Joe Wheat, MD*

Case Report

Colleagues, fungal meningitis is often difficult to recognize and diagnose expeditiously. Among the endemic mycoses, *Blastomyces* meningitis is the least common and the diagnostic approach the least understood.

What do you think is the most sensitive test for diagnosis?

1. Culture
2. Pathology
3. Molecular
4. Antigen detection
5. Antibody detection

A recently published case report and literature review provides insight into the diagnostic approach, which we have supplemented with literature and data from MiraVista Diagnostics.

A recent publication described diagnosis of central nervous system (CNS) blastomycosis by antigen detection of the cerebrospinal fluid (CSF)[1]. An elderly man was hospitalized with meningitis. He was suspected to have pulmonary tuberculosis and was empirically treated with a rifampin-based regimen. A rash developed that was characterized by keratotic nodules with a granulomatous appearance. Skin biopsy grew *Blastomyces dermatitidis*. Itraconazole was initiated and treatment for tuberculosis was continued.

He was readmitted several months later because of impaired consciousness and right-sided weakness. CSF revealed elevated protein (4.39 g/L), reduced glucose (1.3 mmol/L), and leukocytosis (41 x 106/L), predominantly neutrophils. Magnetic resonance imaging revealed basal meningitis, ventriculitis and hydrocephalus. Treatment for bacterial meningitis was initiated without improvement. Polymerase chain reaction for *Mycobacterium tuberculosis* complex was negative. CSF was positive for *Blastomyces* antigen at 1.81 ng/ml. Antigen was also detected in urine at 0.23 ng/ml.

Liposomal amphotericin B (L-AmB) was started, and antibacterial and anti-tuberculosis treatment was stopped. L-AmB was administered for 12 weeks followed by itraconazole for 12 months. Long-term follow-up was not reported.

Discussion

Fungal infection should be considered in patients with CNS disease of unknown etiology [4]. CNS involvement occurs in 5-10% of patients with blastomycosis [5] and presents as meningitis, meningoencephalitis, epidural abscess, and intracranial mass or abscess [3].

Diagnosis may be difficult. Culture of CSF was positive in less than 10% of cases [3, 6]. Cytopathology and culture of brain tissue or meninges are usually positive [6].

Several cases have been diagnosed by detection of antigen in the CSF. Of cases tested at MiraVista Diagnostics, antigen was detected in the CSF in 6 of 7 cases (86%) (Table). Cases have also been diagnosed based on detection of antibodies to *Blastomyces* in the CSF [3].

Table

Case	Culture	Antigen ng/ml	Ref
1	Neg	1.82	[1]
2	Neg	>19.0	[2]
3	Neg	>19.0	[2]
4	None	Neg	[2]
5	Pos	Pos	[3]
6	Neg	Pos	[3]
7	Pos	Pos	[3]

The antigen detected in histoplasmosis and blastomycosis is an immunologically identical galactomannan, so differentiation of the two is impossible. Proof requires isolation of *Blastomyces* by culture or demonstration of *Blastomyces* nucleic acid by molecular methods. A probable diagnosis is established by visualization of 8-20 µM broad-based structures with doubly refractile cell walls by cytopathology or histopathology or detection of antibodies to *Blastomyces*.

Treatment according to IDSA guidelines [7] is reasonably effective. Of 22 patients described in one report, 82% survived [3]. Survival was higher with a lipid formulation of amphotericin B than the deoxycholate formulation (91% versus 73%). In another report, none of 16 patients died of blastomycosis [6]. The favorable experience following the IDSA guideline contrasts to earlier findings in patients treated with prolonged courses of deoxycholate amphotericin B alone, in which 4 of 10 patients died and 1 of 6 survivors relapsed [8].

The IDSA guideline recommends 4 to 6 weeks of a lipid formulation of amphotericin B followed by one year with an azole [7]. Some experts prefer voriconazole because of good CSF penetration [3]. Fluconazole has been used successfully in a few cases [3, 6] but is not preferred, and higher dosages (800 mg daily) are recommended [7]. Itraconazole does not penetrate CSF but penetrates brain tissue and has been used successfully for treatment of CNS histoplasmosis [9] and coccidioidomycosis [10].

In summary, a fungal etiology should be considered in patients with undiagnosed CNS disease or with systemic or pulmonary blastomycosis who manifest CNS findings. Antigen detection provides a rapid, sensitive, noninvasive method for diagnosis, but does not distinguish histoplasmosis and blastomycosis. Antibody detection by enzyme immunoassay may aid in differentiating histoplasmosis [2] and blastomycosis [11] and support the diagnosis in patients with negative antigen results. Cytopathology and culture of CSF are insensitive but often are positive in non-CNS tissues or respiratory secretions. Biopsy of brain or meninges for histopathology and culture may be required for diagnosis in rare cases.

Reference List

(1) Walkty A, Keynan Y, Karlowsky J, Dhaliwal P, Embil J. Central nervous system blastomycosis diagnosed using the MVista(R) Blastomyces quantitative antigen enzyme immunoassay test on cerebrospinal fluid: A case report and review of the literature. Diagn Microbiol Infect Dis **2018 Feb**; 90(2):102-4.

(2) Bloch KC, Myint T, Raymond-Guillen L, et al. Improvement in Diagnosis of Histoplasma Meningitis by Combined Testing for Histoplasma Antigen and Immunoglobulin G and Immunoglobulin M Anti-Histoplasma Antibody in Cerebrospinal Fluid. Clin Infect Dis **2018 Jan 6**; 66(1):89-94.

(3) Bariola JR, Perry P, Pappas PG, et al. Blastomycosis of the central nervous system: a multicenter review of diagnosis and treatment in the modern era. Clin Infect Dis **2010 Mar 15**; 50(6):797-804.

(4) Goralska K, Blaszkowska J, Dzikowiec M. Neuroinfections caused by fungi. Infection **2018 Aug**; 46(4):443-59.

(5) Smith JA, Gauthier G. New Developments in Blastomycosis. Semin Respir Crit Care Med **2015 Oct**; 36(5):715-28.

(6) Bush JW, Wuerz T, Embil JM, Del Bigio MR, McDonald PJ, Krawitz S. Outcomes of persons with blastomycosis involving the central nervous system. Diagn Microbiol Infect Dis **2013 Jun**; 76(2):175-81.

(7) Chapman SW, Dismukes WE, Proia LA, et al. Clinical Practice Guidelines for the Management of Blastomycosis: 2008 Update by the Infectious Diseases Society of America. Clin Infect Dis **2008 May 5**; 460:1801-12.

(8) Kravitz GR, Davies SF, Eckman MR, Sarosi GA. Chronic blastomycotic meningitis. Am J Med **1981 Sep**; 71(3):501-5.

(9) Wheat J, Myint T, Guo Y, et al. Central nervous system histoplasmosis: Multicenter retrospective study on clinical features, diagnostic approach and outcome of treatment. Medicine (Baltimore) **2018 Mar**; 97(13):e0245.

(10) Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis. Clin Infect Dis **2016 Jul 27**.

(11) Richer SM, Smedema ML, Durkin MM, et al. Development of a Highly Sensitive and Specific Blastomycosis Antibody Enzyme Immunoassay Using Blastomyces dermatitidis Surface Protein BAD-1. Clin Vaccine Immunol **2014 Feb**; 21(2):143-6.