Diagnostic Dilemma in Primary *Blastomyces dermatitidis* Meningitis: Role of Neurosurgical Biopsy

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**Key Words**
Central nervous system blastomycosis · Fungal meningitis · Neurosurgical biopsy · Leptomeningeal enhancement

**Abstract**
A 52-year-old male on chronic prednisone for polymyalgia rheumatica presented with a subacute history of headaches, nausea, phonophobia, intermittent diplopia and gait instability. He was hospitalized 2 weeks prior to presentation with extensive evaluations only notable for leptomeningeal inflammation on MRI. His symptoms progressively worsened and he developed aphasia. He was transferred to our facility where extensive spinal fluid examinations were repeated and were again nondiagnostic. Ultimately, a diagnostic skull-based biopsy was performed which demonstrated *Blastomyces dermatitidis* fungal meningitis. Despite extensive sampling and cultures, only 1 of the intraoperative samples yielded diagnostic results. This underscores the low sensitivity of current methods to diagnose CNS blastomycosis. This case suggests that a neurosurgical biopsy may be necessary and should be considered early in the diagnostic process, especially if a definitive diagnosis is elusive. If a biopsy is performed, sampling should be ample and from multiple areas. Following the diagnosis, our patient was treated with liposomal amphotericin B and then voriconazole with a good clinical response.

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**Introduction**
Fungal meningitis is rare and difficult to diagnose. The diagnosis is often delayed due to the poor sensitivity of current detection methods. Neurosurgical biopsy is often considered a
last resort in cases of high clinical suspicion and negative testing. This case report suggests that early diagnostic neurosurgical intervention is appropriate in such cases. It also highlights the fact that even direct intraoperative sampling of areas of inflammation and apparent fungal growth will not guarantee a definitive diagnosis. Therefore, multiple areas must be sampled and the largest volumes taken in order to increase sensitivity and justify such an invasive diagnostic procedure.

**Case Presentation**

The patient is a 52-year-old right-handed male with a medical history of vitiligo, obstructive sleep apnea and polymyalgia rheumatica (PMR) for which he was maintained on chronic oral prednisone. Approximately 3 weeks prior to presentation at our institution, he had an insidious onset of a pulsating bitemporal, bioccipital positional headache which worsened when he assumed a supine position. This progressed to include nausea, intermittent diplopia, phonophobia and gait instability. The patient’s wife also noted a significant decrement in his short-term memory and executive functions.

He presented to his local emergency department. An MRI with and without IV contrast showed left basilar leptomeningeal enhancement prompting a lumbar puncture. Cerebrospinal fluid (CSF) analysis revealed elevated protein, hypoglycorrhachia, pleocytosis with lymphocytic predominance, negative gram stain, a bacterial culture and cytology. In addition, a complete metabolic panel revealed hyponatremia, international normalized ratio and activated partial thromboplastin time, elevated total bilirubin and elevated inflammatory biomarkers. He was treated with a course of antibiotics and sent home. His symptoms continued to worsen and he presented to his local emergency department a week later and was again discharged home.

Approximately 1 week after this second discharge, he experienced a sudden onset of left facial and arm weakness with a reduced verbal output. He was able to follow commands during this time though. He presented to our institution and on arrival, he had begun to show a symptomatic improvement of the left face and arm weakness. On review of symptoms, he endorsed chills occurring daily at about 4 a.m. but denied fever, diaphoresis, numbness, tingling, dysphagia, dysarthria, visual disturbances, chest pain, shortness of breath, abdominal pain, or urinary symptoms. A neurological examination showed left lower motor neuron facial weakness with a House-Brackmann score of 2, dysarthria and diffuse hyperreflexia with bilateral Hoffmann’s signs. Otherwise, the rest of his examination, including cranial nerves, was unremarkable.

**Diagnostic Tests**

*Laboratory Findings*

The laboratory findings are summarized in the tables. Briefly, on initial presentation to our institution, a serum analysis revealed profound hyponatremia, mild normocytic anemia and mildly elevated inflammatory markers (table 1).

A spinal fluid analysis was repeated on initial presentation to our facility as well. His spinal fluid was grossly bloody with an elevated protein of 534 mg/dl and hypoglycorrhachia (glucose of 26 mg/dl). Blastomyces, coccidioides, histoplasma PCR and cryptococcus antigens were tested. Blastomyces PCR and cryptococcus antigen tests were negative. Initial coccidioides and histoplasma antibody screens were reactive, but reflex confirmatory tests
for these pathogens were negative. *Mycobacterium tuberculosis* PCR, mycoplasma PCR and lyme PCR were all negative as well (table 2).

A repeat lumbar puncture 2 days after the initial presentation was less bloody, but remained hypercellular with 393 nucleated cells (46% lymphocytes). Protein and glucose levels similarly remained abnormal. Cytology and flow cytometry were performed on this sample and were negative. Histoplasma, blastomyces, and coccidioides PCR were again negative.

The analysis was broadened to include immunologic and paraneoplastic markers as shown in table 2. All immunologic and paraneoplastic markers were negative (table 2).

**Imaging**

A brain MRI confirmed extensive nodular leptomeningeal enhancement along the left ventral medulla, and pons becoming more circumferential around the midbrain with disease extension into the left Sylvian fissure and along the pituitary infundibulum (fig. 1). A CT scan of the chest showed multiple small, noncalcified pulmonary nodules in the left upper and right lower lobes. There was no pleural effusion or adenopathy, and a whole-body FDG PET CT scan was negative. An abdominal CT demonstrated only a tiny hepatic cyst.

**Biopsy**

As the extensive workup remained inconclusive, the patient underwent a left far-lateral occipital craniotomy and C1 laminectomy with multiple biopsies of the brain stem and cerebellopontine angle with operative microscope and intraoperative stereotaxis. The arachnoid was thick with what appeared to be fungal colonies. These were sampled and a portion was removed and sent for pathology and cultures. Colonies were also noted to encompass the cerebellopontine angle, vertebral artery and cervical spinal accessory nerves. These were carefully dissected and multiple samples were sent off for pathological analysis. An example of an intraoperative mycotic mass is shown in figure 2.

**Pathology**

Intraoperative samples included left medullary masses (1–4), CSF, C1 arachnoid, C1 arachnoid mass, C1 white matter, jugular foramen mass, subdural space at jugular tubercle swab, cervical spinal accessory mass, spinal cervical mass 1 and 2, tonsillar arachnoid (1–2), cervical medullary arachnoid 1 and 2, GMS and PAS stains of the tonsillar arachnoid No. 1 and left medullary mass No. 3 revealed necrotizing granulomatous inflammation with yeast forms, morphologically consistent with blastomyces. C1 arachnoid mass and jugular foramen mass swab ultimately grew blastomyces after 16 days of fungal culture. All other samples had negative GMS and PAS stains and did not grow organisms after 60 days of culture despite similar gross appearance to the positive samples. Fite stain for acid fast bacilli were negative on all samples.

**Treatment and Outcome**

Once the diagnosis was confirmed, the patient was started on daily infusions of liposomal amphotericin B, and steroids were tapered. He had a remarkable improvement in his symptoms. His headaches abated after only 2 days of therapy and his hyponatremia, felt to be due to SIADH from hypothalamic involvement, resolved. He was discharged with a plan for long-term antifungal therapy after 4 days of inpatient treatment. However, amphotericin B was discontinued and he was transitioned to voriconazole after only 17 days of therapy due to acute kidney injury.
A follow-up at 3 months revealed only mild right facial palsy. His MRI was significant for interval decrease in nodular enhancement along the left ventral medulla and pons, around the midbrain and into the left sylvian fissure with a near complete resolution of associated T2 hyperintensity in the brain parenchyma adjacent to the areas of residual enhancement.

Discussion

Blastomycosis is an exceedingly rare cause of subacute to chronic meningitis with clinically apparent CNS involvement occurring in only 5–10% of cases [1]. Isolated CNS involvement has been reported but remains controversial [2] as exemplified in 1 recent report [3], in which it is unclear whether the scope of investigative studies performed were sufficient to definitively exclude systemic disease. It is possible that ‘incidental’ radiographic or laboratory findings such as elevated liver function studies [2] or pulmonary nodules such as those present in our patient, are the result of systemic blastomycosis. Certainly, the presence of pulmonary nodules raised our suspicion for a fungal/infectious etiology and helped to focus and expedite the diagnostic process.

Differential

Differential diagnosis for a subacute to chronic basilar meningitis includes infectious etiologies such as fungi and tuberculosis, inflammatory etiologies such as neurosarcoidosis and neoplastic etiologies such as meningeal carcinomatosis or lymphoma. The pulmonary findings of multiple nodules on CT as well as the constitutional symptoms suggested an infectious etiology. However, as the patient had already undergone extensive evaluation for fungal meningitis (including CSF analysis from a total of 4 lumbar punctures), other etiologies were considered, especially autoimmune (neurosarcoidosis and idiopathic hypertrophic pachymeningitis) and neoplastic (leptomeningeal carcinomatosis and lymphoma).

Diagnostic delay continues to be of major concern in the management of blastomycosis. In cases of primary CNS involvement lacking clinically apparent systemic features and easily accessible targets for biopsy, a constellation of additional factors contributes to further delays with diagnosis and timely intervention often resulting in catastrophic results.

The chronicity and lack of specificity associated with these symptoms and the frequent inability of the patient to provide a reliable history renders the clinician heavily dependent on imaging, serological and microbiological studies. For example, in a recent study of 22 patients with CNS blastomycosis, the most common symptom was chronic headache (86%) [4]. The urgency with which tests are performed is often dependent on the degree of clinical suspicion for blastomycosis or other fungal infections. The majority of patients with fungal meningitis are symptomatic for more than a month before the diagnosis is made [5]. More disturbingly, in 1 report, autopsy-confirmed blastomycosis was suspected in only one third of patients who eventually succumbed to this treatable disease [6].

Culture is the current gold standard for the diagnosis of blastomycosis. Sensitivities of 86 and 92% from sputum and bronchoscopic specimens, respectively, are reported [7]. However, the sensitivity of CSF culture is under 50% [4]. The diagnostic yield is thought to be improved when CSF is sampled directly from the ventricles, but the increase in sensitivity appears to be marginal [2]. Neurosurgical biopsy has been employed with good success in securing the diagnosis, but this is often performed as a last resort after other tests failed to yield a diagnosis [3, 4, 8]. In the present case, CSF obtained from lumbar puncture provided no diagnostic utility with culture, PCR and antigen testing, all producing false negative results. Surprisingly, fungal smear, culture, PCR and antigen studies of tissue or CSF samples
obtained directly from or adjacent to fungal masses intraoperatively, including direct swabs of a left medullary mycotic-appearing mass (fig. 2), were nondiagnostic. Only the sample obtained from the adjacent jugular foramen grew B. dermatitidis.

This case underscores the importance of a more central role for neurosurgery in CNS blastomycosis. A biopsy should be performed early as the diagnostic yield from nonsurgical samples remains low despite recent advances in molecular and immunological methods. Furthermore, when performing a biopsy, multiple mycotic lesions and CSF must be sampled from disparate areas as the correlation between gross examination and diagnostic yield is also uncertain. This is likely due to the fact that the gross lesions are the result of central granulomatous inflammation and not necessarily areas in which there is a high density of B. dermatitidis organisms per se. The predilection of CNS blastomycosis to cause inflammation of the basilar leptomeninges places a limit on the scope of neurosurgical exploration and sampling particularly when the patient has no focal neurological deficits and the procedure is thus deemed purely diagnostic. The treatment of choice, liposomal amphotericin B, carries significant toxicity risks, so a definitive diagnosis is essential. Thus, a balance needs to be established between sufficient tissue sampling and the principle of primum non nocere.

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**Table 1.** List of basic labs and CSF analysis performed on initial presentation to our institution

| Basic laboratory tests                          | Value | Reference range |
|------------------------------------------------|-------|-----------------|
| Albumin, g/dl                                   | 4.7   | 3.5–5.0         |
| Alkaline phosphatase, U/l                       | 65    | 45–115          |
| ALT, U/l                                        | 12    | 7–55            |
| AST, U/l                                        | 16    | 8–48            |
| Bicarbonate, mmol/l                             | 24    | 22–29           |
| Chloride, mmol/l                                | 82    | 98–107          |
| Creatinine, mg/dl                               | 0.7   | 0.8–1.3         |
| CRP, mg/l                                       | 30    | <8              |
| ESR, mm/h                                       | 35    | 0–22            |
| Glucose, mg/dl                                  | 98    | 70–140          |
| Hemoglobin, g/dl                                | 12.9  | 13.5–17.5       |
| K, mmol/l                                       | 4.4   | 3.6–5.2         |
| Na, mmol/l                                      | 120   | 135–145         |
| Total bilirubin, serum, mg/dl                   | 1.4   | 0.1–1.0         |
| WBC, ×10⁹/l                                     | 9     | 3.5–10.5        |
| CSF analysis                                    |       |                 |
| Opening pressure, mm H₂O                        | 250   | 50–180          |
| Gross appearance                               | bloody | clear         |
| Total nucleated cells                           | 231   | 0–5             |
| Lymphocytes, %                                  | 12    | ≤70             |
| Monocytes/macrophages, %                        | 1     | ≤30             |
| Neutrophils, %                                  | 87    | 0–6             |
| Total protein, mg/dl                            | 565   | 0–35            |
| Albumin, CSF, mg/dl                             | 692   | <27             |
| Albumin, S, mg/dl                               | 4,680 | 3,200–4,800     |
| Glucose, CSF, % serum glucose                   | 26    | >60             |
| Angiotensin converting enzyme, U/l              | 2.6   | 0–2.5           |
| IgG, CSF, mg/dl                                 | 140   | <8.1            |
| IgG, S, mg/dl                                   | 901   | 767–1,590       |
| CSF IgG Index,                                  | 1.05  | <0.85           |
| LDH, CSF                                        | 34    | 1/10th serum    |
| LDH, S, U/l                                     | 15.1  | 122–222         |
| Synthesis rate, mg/24 h                         | 411.82| <12             |
| Miscellaneous tests                             |       |                 |
| TPO antibodies, IU/ml                           | 291.3 | <9              |
| TSH, Serum, mIU/l                              | 2     | 0.3–5.0         |
| Vitamin B₁₂ Assay, S, ng/l                     | 812   | 180–914         |

Values outside the reference range have been bolded. ALT = Alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.
Table 2. Infectious and immunologic testing obtained during diagnostic evaluation

| Infectious disease testing | Immunologic testing |
|---------------------------|---------------------|
| Aspergillus Ag, S         | AChR binding Ab, S  |
| Blastomyces Ab, EIA, CSF  | AChR ganglionic neuronal Ab, S |
| Blastomyces Ab, EIA, S    | AGNA-1, S           |
| Coccidioides Ab screen, CSF | Amphyphysin Ab, S   |
| Coccidioides Ab, CF CSF   | ANA Ab              |
| Coccidioides Ab, S        | ANNA-1, S           |
| Coccidioides IgG immunodiffusion | ANNA-2, S        |
| Coccidioides IgM immunodiffusion | ANNA-3, S   |
| Cryptococcus Ag screen    | Complement, C3, S   |
| Eastern equine encephalitis, CSF | Complement, C4, S   |
| Histoplasma Ab screen, CSF| Complement, total, S|
| Histoplasma immunodiffusion| CRMP-5 IgG, S     |
| Histoplasma -mycelia, S   | CRP                 |

Infectoplasma/blastomyces PCR, (CSF, Arachnoid C1) | Cyclic citrullinated peptide Abs |
Histoplasma-yeast, CSF | Jo 1 Ab, IgG, S |
HIV-1/2 Ag and Ab screen, S | MPO Ab |
IgG Calif virus (LaCrosse) Ab | Neuronal (V-G) K+ channel Ab, S |
IgM Calif virus (LaCrosse) Ab | N-type calcium channel Ab |
Lyme disease ELISA | P/Q-type calcium channel Ab |
Lyme disease serology, CSF | PCA-1, S |
M. tuberculosis complex PCR, CSF | PCA-2, S |
M. tuberculosis complex quantiferon, CSF | PCA-Tr, S |
MVista blastomyces quantitative antigen, urine | Proteinase (PR3) |
Sporothrix Ab, CSF | Rheumatoid factor |
Sporothrix Ab, S | RNP Ab, IgG, S |
St. Louis encephalitis IgG Ab, CSF | Scl 70 A, IgG, S |
St. Louis encephalitis IgM Ab, CSF | Sm Ab, IgG, S |
Syphilis IgG, S | SS-A/Ro Ab, IgG, S |
VDRL | SS-B/La Ab, IgG, S |
West equine encephalitis A | Striated muscle Ab |

β2 microglobulin, S

Infectious (left column) and immunologic (right column) tests performed during diagnostic evaluation. S or CSF indicates testing performed on serum or CSF samples, respectively. The coccidioides and histoplasma Ab screens in CSF were initially positive, but all confirmatory tests were negative. Ab = Antibody; AChR = acetylcholine receptor; Ag = antigen; AGNA-1 = anti-glial nuclear antibody 1; ANA = anti-nuclear antibody; ANNA = anti-neuronal nuclear antibody; CRMP-5 = collapsin response mediator protein 5; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; MPO = myeloperoxidase; PCA = Purkinje cell cytoplasmic antibody; PCR = polymerase chain reaction; RNP = ribonudeoprotein; Scl = scleroderma.
Fig. 1. Gadolinium-enhanced T1 MRI shows left medullary enhancement (arrow, a) as extensive nodular circumferential leptomeningeal enhancement (arrows, b). Findings correlate with axial T2 FLAIR images also showing lateral brainstem hyperintensity (arrows, c) as well as a patchy involvement of the bilateral midbrain (arrows, d) and the pituitary infundibulum (arrowhead, d).

Fig. 2. Intraoperative photograph shows the direct swab of a mycotic-appearing mass which resulted in negative smear and culture. Also seen are a number of small colonies (arrowheads), one of which resulted in the positive identification of Blastomyces dermatitidis on culture.