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Disseminated blastomycosis with an intracranial fungoma in an immunocompetent patient: illustrative case

Annabelle Shaffer, MS,[1] Ryan Johnson, DO,[2] Gina Guglielmi, DO,[2] Anant Naik, BS,[1] Daniel Najafali, BS,[1] Amir A. Khan, MD,[1,3] Frank J. Bellafiore, MD,[4] Paul M. Arnold, MD,[1,2] and Wael Hassaneen, MD, PhD[1,2]

[1]Carle Illinois College of Medicine, University of Illinois Urbana Champaign, Urbana, Illinois; and Departments of [2]Neurosurgery, [3]Infectious Diseases, and [4]Pathology, Carle Foundation Hospital, Urbana, Illinois

BACKGROUND *Blastomyces dermatitidis* is a fungus endemic to central and southern North America. While infection most commonly results in pneumonia, a small number of infections progress to systemic disease, which may include intracranial lesions. Progression to systemic disease is most common in immunocompromised patients, such as those with human immunodeficiency virus.

OBSERVATIONS The authors present a 44-year-old immunocompetent male who presented following a tonic-clonic seizure. Initial workup revealed a 19-mm enhancing intracranial mass. There was avid uptake of fluorescein sodium, and an en bloc resection of the mass was performed. Histopathology revealed *B. dermatitidis.* Medical management included amphotericin B and azole therapy. Postoperative recovery was uneventful, and no focal neurological deficits were appreciated.

LESSONS This case highlights the neurosurgical management of a rare intracranial fungal manifestation in an immunocompetent patient. A literature review was also performed to better understand the role of neurosurgery in fungal infections. There were limited cases of intracranial *Blastomyces* reported in immunocompetent patients, and neurosurgical management varied (no intervention, biopsy, resection) and was underreported. Too few cases are reported to suggest neurosurgical intervention for blastomycosis improves outcomes. Medical management was relatively standard with azole and amphotericin therapy.

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KEYWORDS blastomycosis; central nervous system; intracranial mass; fungoma

Blastomyces dermatitidis is a dimorphic fungus endemic to central and southern North America,[1] for which epidemiological patterns are not fully elucidated.[2] Infection most commonly results in pneumonia but can infect the skin, bones, and the genitourinary tract.[1] In 5%–10% of cases, *Blastomyces* can involve the central nervous system (CNS), leading to meningitis, intracranial abscesses, seizures, and altered mental status, predominantly in immunocompromised patients.[3] Utilizing contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), CNS abscesses can mimic metastasis or primary glioma due to their ring-enhancing profile.[4–6] Mimicry can lead to delays in diagnosis and treatment, which were significantly associated with death in a prior study.[7] There is a paucity of data available for the management of intracranial *Blastomyces* in immunocompetent patients. Here we report a case of disseminated blastomycosis with CNS involvement in an immunocompetent male managed with resection.

Illustrative Case

A 44-year-old male presented with no notable past medical history. He denied drug use, reported frequent work outdoors, and was negative for human immunodeficiency virus (HIV). He had presented to an outside emergency department following a new-onset witnessed generalized tonic-clonic seizure with loss of consciousness lasting 30 seconds followed by up to 15 minutes of postictal confusion. CT of the brain at an outside hospital demonstrated an 18-mm hyperdense, hemorrhagic lesion in the left frontal lobe with

ABBREVIATIONS CNS = central nervous system; CT = computed tomography; HIV = human immunodeficiency virus; IV = intravenous; MRI = magnetic resonance imaging.

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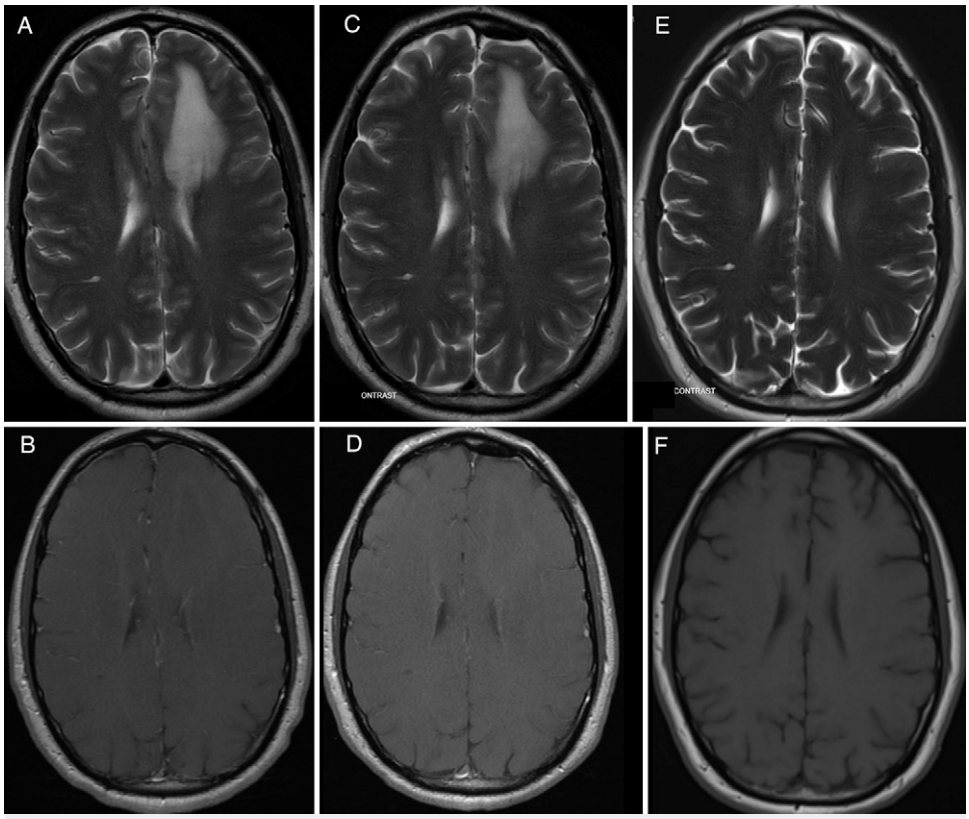

FIG. 1. Preoperative T2-weighted MRI with contrast (**A**) demonstrated a lesion in the left frontal lobe. Preoperative T1-weighted MRI with contrast (**B**). Postoperative T2-weighted MRI with contrast (**C**) demonstrating resection cavity, stable mass effect, and vasogenic edema. Postoperative T1-weighted MRI with contrast (**D**). Three-month postoperative T2-weighted MRI with contrast (**E**). Three-month postoperative T1-weighted MRI without contrast (**F**). Gadolinium contrast was utilized where noted.

significant vasogenic edema. Upon transfer to our community hospital, he was started on steroids and seizure prophylaxis. Mild head pain without notable neurological deficits was noted on physical examination. The electroencephalogram was normal. MRI of the brain demonstrated a heterogeneously enhancing mass centered within the left frontal lobe measuring 17 mm anterior-posterior × 19 mm transverse × 19 mm cranial-caudal and mild central diffusion restriction (Fig. 1A). Extensive vasogenic edema was present without significant midline shift or acute hydrocephalus. CT of the chest and abdomen demonstrated predominant ground-glass nodularity bilaterally, splenomegaly, medial hypo-enhancing splenic lesion, and peripherally enhancing lesion in gluteal subcutaneous fat.

A left frontal craniotomy was performed utilizing StealthStation (Medtronic) navigation, fluorescence-guided resection, and an operative microscope. A firm encapsulated mass with avid uptake of fluorescein sodium was identified and resected en bloc (Fig. 2). The intraoperative frozen section favored *Cryptococcus* fungi. Postoperatively, the patient had a mild headache without notable neurological deficits. MRI of the brain demonstrated stable, mild mass effect and vasogenic edema (Fig. 1B).

He was started on fluconazole for fungal coverage while a definitive diagnosis could be made. Cryptococcal and histoplasma antigens were confirmed negative with Karius digital culture. *Blastomyces* was also detected on Karius digital culture (65 DNA particles/μL). Initial *Blastomyces* antigen was >20.0 ng/mL (Fig. 3). Following diagnosis, intravenous (IV) amphotericin B was added to the treatment regime. A lumbar puncture was not recommended due to cerebral edema. Upon discharge, he received daily outpatient IV liposomal amphotericin B for

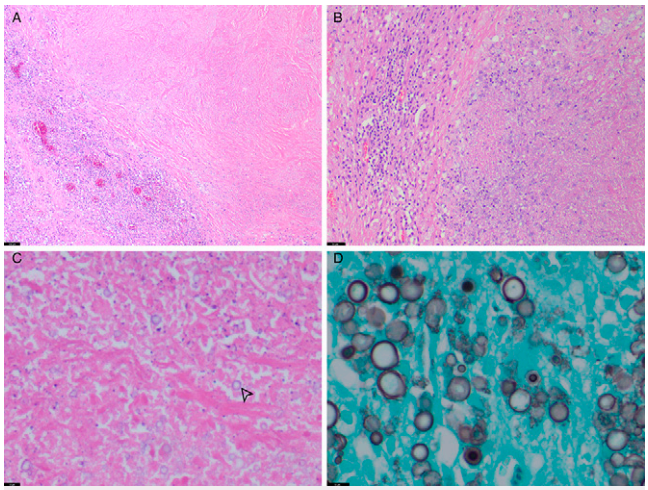

FIG. 2. Histopathology of the fungoma: hematoxylin and eosin (H&E) ×100 μm (**A**), H&E ×50 μm (**B**); rounded yeast (*arrowhead*) larger than neutrophils, H&E ×10 μm (**C**); broad-based budding, Silver stain ×10 μm (**D**).

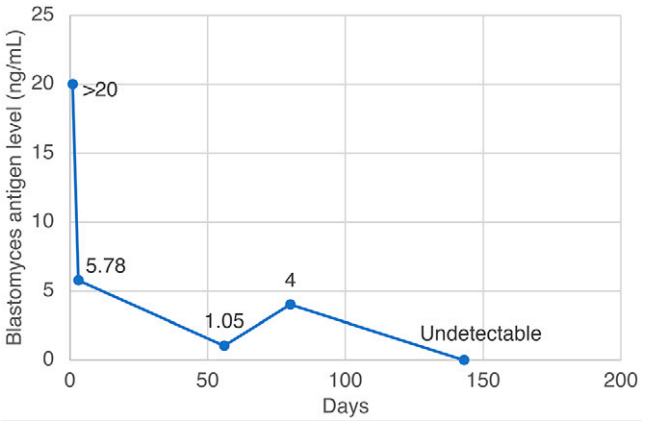

FIG. 3. *Blastomyces* antigen levels.

4 weeks. Due to declining renal function, he was switched to oral voriconazole. At the last follow-up, he was without neurological deficits and continued to take oral voriconazole (Fig. 1C).

Discussion

Observations

Here, we present an immunocompetent male patient with disseminated blastomycosis managed aggressively with gross total resection and subsequent antifungal therapy. This case adds to the small body of literature on CNS blastomycosis and sheds light on the neurosurgical management of the disease. A systematic search was performed to identify cases of intracranial fungomas due to *Blastomyces* in immunocompetent patients, and 2 authors independently reviewed articles for inclusion (Fig. 4). We considered patients immunocompetent if they were HIV-negative and did not have significant chronic diseases.

CNS *Blastomyces* has been previously reported in case reports and small, retrospective studies[3,4,6,8,9] (Table 1). Neurological symptoms and enhancing lesions on brain MRI were common.[4–6] In our case and those presented by Slomka and Doub[4] and Munich et al.,[6] a solitary enhancing lesion was appreciated; however, Goico et al.[9] presented a case in which several small enhancing lesions were appreciated indicating the presentation can vary substantially. Despite the variability between intraparenchymal and leptomeningeal lesions, MRI provides better diagnostic utility given the various reports of CT-negative findings in patients with confirmed intracranial *Blastomyces*.[10] The diagnostic utility of other MRI modalities has also been explored in limited studies, notably MR spectroscopy, which has shown trehalose peaks consistent with the presence of other intracranial fungomas.[10]

Diagnosis of disseminated *Blastomyces*, both extracranially and intracranially, can be made by direct lesion biopsy,[3,4,6,8] culture of cerebrospinal fluid,[3,8] blood, or bronchoalveolar lavage fluid,[9] and testing for antigen presence in the blood. Whether intracranial or extracranial, the isolation of *Blastomyces* spp. in culture is considered

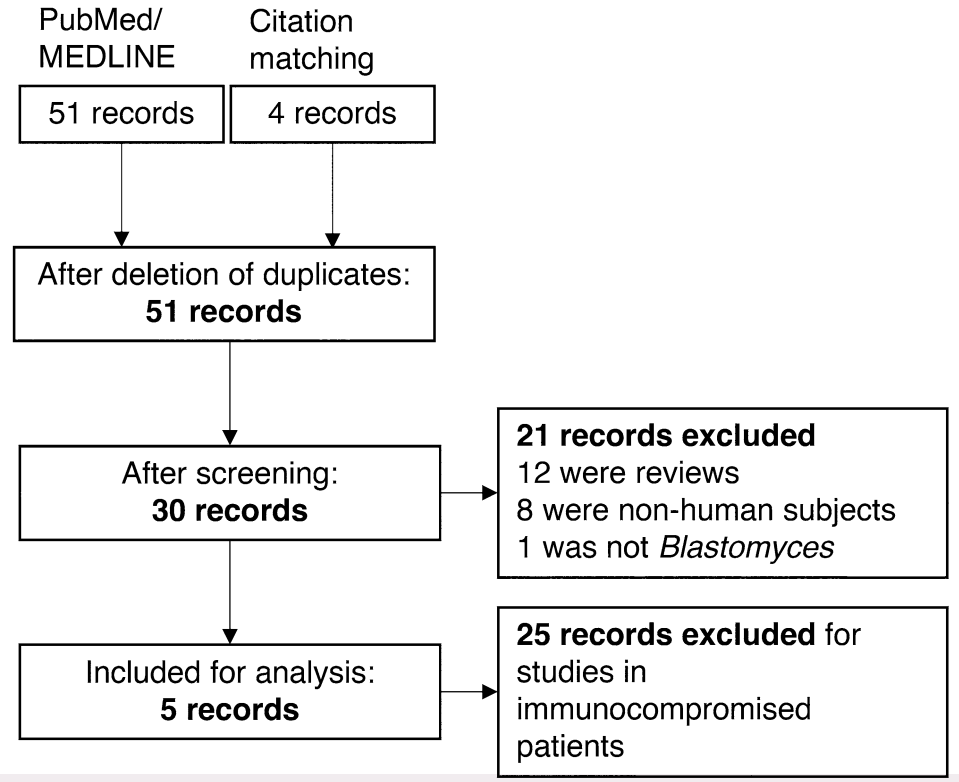

FIG. 4. Flow diagram demonstrating systematic review of evidence. Fifty-one records were identified on PubMed/MEDLINE, with an additional 4 records identified via citation matching. Twenty-one records were excluded after reviewing abstract and title information. Twenty-five records were additionally excluded after full record review for immunocompetence of patients.

TABLE 1. Review of cases in the literature

Authors & Year	Pt Characteristics	Histological Findings	Management	Outcome
Bariola et al., 2010[8]	A multicenter retrospective study identified 10 pts w/ CNS blastomycosis w/o immunosuppression. All pts presented w/ neurological symptoms.	Diagnosis of *Blastomyces* was achieved w/ CSF culture &/or Bx	Pts were managed w/ amphotericin B w/ azole therapy or flucytosine; 6 pts underwent brain Bx.	Two pts died due to blastomycosis.
Bush et al., 2013[3]	12 cases of confirmed or probable CNS blastomycosis in pts w/o comorbidities. Headache & focal neurological deficit were the most common presenting features.	Diagnosis of *Blastomyces* was achieved w/ CSF culture &/or Bx	Pts were managed w/ amphotericin B & azole therapy. CNS parenchyma was biopsied in some pts; no further neurosurgical management was described.	All surviving pts are in remission.
Munich et al., 2013[6]	63-yr-old male w/ prior non-Hodgkin's lymphoma (9 years ago) presenting w/ persistent nausea & vomiting. After gastrointestinal causes were ruled out, an enhancing rt cerebellar lesion was identified along w/ obstructive hydrocephalus.	A cystic avascular brain mass w/ yellow fluid was resected. Pathology revealed *Blastomyces*.	Gross total resection via suboccipital craniotomy was performed. The pt was managed w/ amphotericin B & azole therapy.	Pt has mild ataxia without evidence of recurrence at 1 mo.
Goico et al., 2018[9]	36-yr-old immunocompetent male presenting w/ paresthesia, hemoptysis, fever, weight loss.	Bronchoalveolar lavage used for diagnosis.	Pt was initially managed for tuberculosis, but later treated for blastomycosis. MRI of the brain demonstrated several small enhancing lesions. Pt was treated w/ liposomal IV amphotericin followed by azole therapy.	Pt achieved resolution of imaging features & continues to be asymptomatic after 1 yr.
Slomka & Doub, 2020[4]	41-yr-old immunocompetent female presenting w/ new onset Sz. Rt parieto-occipital enhancing mass identified (23 mm $\times$ 20 mm $\times$ 18 mm).	Initial Bx was suspicious for a free-living amoebic infection; however, Blastomyces was later identified w/ mass spectrometry & next-generation sequencing.	She was initially managed for concern of neoplasm. Bx was obtained 5 weeks later after Sz recurrence. She was treated w/ voriconazole, but progression was noted, & resection was performed. The pt was managed w/ amphotericin B & azole therapy.	No recurrence was noted on MRI 2 mo following resection. Pt is reportedly in her usual state of health. Fluconazole therapy is scheduled to continue for 1 yr.

Bx = biopsy; CSF = cerebropinal fluid; pt = patient; Sz = seizure.

definitive. Histopathology and cytology can also be diagnostic by demonstrating thick-walled yeasts with a single daughter cell attached with a broad base. Antibody testing, namely with the BAD-1 marker, has also been used to supplement diagnosis, with an 88% sensitivity and 99% specificity. Antigen testing and polymerase chain reaction studies are still experimental, with large studies needing to validate their diagnostic efficacy.[11]

Neurosurgical management was scarcely reported. Slomka and Doub[4] and Munich et al.[6] describe 2 cases in which the fungal mass or abscess was resected, while Bush et al.[3] and Bariola et al.[8] describe cases where a brain biopsy was performed. In cases where resection occurred, all patients were in remission at the last known follow-up. Similarly, surviving patients without resection are in remission. Previous reporting of intracranial fungal granulomas, predominantly aspergillosis, suggests that mortality has decreased in recent years: Naik et al.[12] reported a mortality rate of 36.3%, while Lin et al.[13] reported 88.1% mortality, which may be due to improvements in surgical management and

antifungal medications. In Naik et al.,[12] radical excision of intracranial fungomas followed by antifungal therapy was performed in nearly all cases, and complications included infarcts, cavernous sinus thrombosis, meningoencephalitis, and ventriculitis. Additionally, meningoencephalitis is a common cause of death,[12,14] and recurrence of fungomas is noted in multiple cases.[12] Antifungal therapy commonly included formulations of amphotericin B and azoles (Table 1). In 2008, the Infectious Diseases Society of America issued guidelines for managing *Blastomyces*, including cases of systemic infiltration.[10] Itraconazole, fluconazole, and voriconazole were included equivocally in their recommendations, although, more recently, studies have demonstrated the utility of voriconazole over other formulations for CNS dissemination of fungal infections due to improved CNS penetration of the medication.[15]

Lessons

In this case, gross total resection of the fungoma was performed. The patient had an uncomplicated recovery, and the fungoma has not recurred. However, too few cases are reported to suggest that neurosurgical intervention for blastomycosis improves outcomes. Blastomycosis may be considered as a differential diagnosis in areas where the fungus is endemic and when the patient is immunocompromised, has respiratory symptoms, or works outdoors. While more common in immunocompromised patients, CNS blastomycosis should not be dismissed based on immunocompetency.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Hassaneen, Shaffer, Najafali, Arnold. Acquisition of data: Shaffer, Khan. Analysis and interpretation of data: Shaffer, Najafali, Khan. Drafting of the article: Shaffer, Johnson, Guglielmi, Naik, Najafali. Critically revising the article: Hassaneen, Shaffer, Johnson, Naik, Najafali, Khan, Arnold. Reviewed submitted version of manuscript: Shaffer, Johnson, Najafali, Arnold. Approved the final version of the manuscript on behalf of all authors: Hassaneen. Study supervision: Hassaneen, Naik, Najafali, Khan. Pathologic diagnosis, workup, and microscopic photos: Bellafiore.

Correspondence

Wael Hassaneen: Carle Neuroscience Institute, Carle Foundation Hospital, Urbana, IL. wael.mostafa@carle.com