Case Report

Fungal brain abscess caused by “Black Mold” (Cladophialophora bantiana) – A case report of successful treatment with an emphasis on how fungal brain abscess may be different from bacterial brain abscess

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Abstract

Background: Central nervous system infection with Cladophialophora bantiana (Black Mold) is rare. It carries a high mortality rate, that is more than 70%, despite multimodal therapy.

Case Description: We present a rare case of “black mold” fungal brain abscess that was successfully treated with good patient outcome. The case is unusual because there were two fungal brain abscesses located bilaterally symmetrically in the mesial frontal lobes, and the response to different treatment strategies was well documented by over 25 magnetic resonance imaging (MRI) scans. Initial attempts to treat these lesions by repeated surgical excision and systemic amphotericin B was followed by continued growth rather than resolution. We realized that the application of treatment principles learned from bacterial brain abscess may not transpose intuitively to the treatment of fungal brain abscess. Therefore, a new treatment strategy was adopted that avoided further attempts at resection in favor of long-term oral voriconazole and repeated intracavitary aspiration and instillation of amphotericin B on an outpatient basis. Without further resection, the lesions stabilized and the aspirates eventually sterilized, however, the enhancing capsule never resolved on MRI scans. All treatment was stopped after 1 year. The apparently sterilized lesions have been followed for an additional 3 years without further growth, and the patient remains functionally, intellectually, and behaviorally normal.

Conclusion: We conclude that, in the case of fungal abscess, it may be preferable to sterilize the lesion in situ rather than attempting to achieve resolution on imaging studies by repeated surgical resection of the capsule which can be
INTRODUCTION

Brain abscess caused by the fungus Cladophialophora bantiana (Black Mold) is notoriously difficult to treat with a mortality of over 70% reported in a large series. This high mortality rate is presumed to stem only from the virulence and pathophysiology of the organism itself; however, our experience with a recent case leads us to question the role that currently accepted surgical treatment strategy might have. Specifically, the application of treatment principles learned from decades of refinements in the surgical and pharmacological treatment of bacterial abscess may not transpose intuitively to the treatment of fungal brain abscess. Clearly, fungal brain abscess is different from bacterial brain abscess, and the implications of these differences may not be fully appreciated currently for their implications in optimizing treatment for fungal brain abscess.

The case presented here is unusual in that there were two bilaterally symmetrical abscesses, with subtle differences that may account for their different response to treatment. In addition, there is extensive documentation by frequent MRI scans (25 in total) showing response of both lesions to various surgical and medical treatment attempts. In aggregate, the data appear to show that surgical extracapsular resection can be followed by enlargement of the lesion rather than aiding resolution. Early reformation and continued growth of a new enhancing capsule along the margins of the twice attempted resection was appreciated on one side and led to a change in treatment strategy away from further resection in favor of intracavitary catheter placement for repeated aspiration of pus and instillation of amphotericin B, in addition to oral voriconazole. This strategy accepts that the capsule may be important to the patient’s immune defense against the fungus. Helping that defense barrier with intracapsular and systemic antifungal agents, rather than capsular removal, may be the better strategy for patients in whom early aggressive resection has failed. The basis for the apparent differences in the response of fungal versus bacterial brain abscess to surgical resection is discussed in the light of pathological findings from this and other cases.

Key Words: Abscess, antifungal, black mold, brain, excision

CASE PRESENTATION

Our patient is a 59-year-old right-handed male who presented to us after a new-onset seizure. He had a past medical history of well-controlled type II diabetes mellitus and mild chronic obstructive pulmonary disease. Neurological exam on admission was normal, however, initial imaging of the brain revealed bilateral mesial frontal ring-enhancing lesions most consistent with abscesses [Figure 1]. His initial labs were unremarkable with normal white blood cells, low erythrocyte sedimentation rate 8, and C-reactive protein 1.5. Further evaluation revealed a tooth infection, and his blood cultures came back suggestive of a bacillus. A presumptive diagnosis of bilateral bacterial brain abscesses was made and the patient was started on empiric antibiotics (ceftriaxone and metronidazole).

Magnetic resonance imaging (MRI) of the brain scan with contrast was repeated after 1 week of antibiotics, and the lesions appeared stable. The patient was then discharged home with a PICC line on intravenous Ertapenem and oral Levetiracetam. Four days after discharge, the patient presented with a recurrent seizure. The patient was readmitted to the hospital and placed back on ceftriaxone and metronidazole. Because of the unexpected worsening course, MRI brain was repeated approximately weekly from that point, showing convincing evidence of progression of both lesions at approximately 3 weeks despite antibiotic medication. He was then taken for a bifrontal burr hole craniotomy and...
stereotactic aspiration of both lesions. Pus was retrieved from both lesions which on gram stain did not reveal bacterial but instead showed septated hyphae typical of fungi. Amphotericin B intravenously was then added for coverage [Figure 2]. One week after the stereotactic aspiration, MRI showed that the lesions had enlarged further. The patient was then taken back for bifrontal craniotomy and attempted aggressive total resection by extracapsular removal of both lesions and placement of bilateral intracavitary Ommaya reservoirs.

Two days later, treatment with intracavitary amphotericin B 0.5 mg was started. Cultures later confirmed black mold (dark colored largely unbranched hyphae) C. bantiana species [Figure 3]. Oral voriconazole was started as well as intravenous (IV) amphotericin B. During this hospital stay, the patient developed several complications: Pancreatitis, pneumonia due to gram positive cocci infection, PICC line infection with gram positive cocci, acute kidney injury, and pleural effusion that required drainage with chest tube. IV amphotericin was then permanently stopped but intracavitary amphotericin B and oral voriconazole were continued.

Following surgery, the right lesion reformed an enhancing capsule, which then shrank and stabilized measuring approximately ~2.5 cm³. The left-sided lesion also reformed a capsule and initially continued to enlarge slowly. The left lesion measured 55 cm³ 1 week after resection and progressed to a peak of 66 cm³ at approximately 1 month. During this time, the patient’s neurological exam remained entirely normal, without focal deficits, signs, or symptoms of raised intracranial pressure or meningismus. After the initial post-resection enlargement, both abscesses started to decrease in size on the new regimen. After 2 months in the hospital, the patient had stable brain MRIs and was discharged on oral voriconazole and continued intracavitary aspiration with amphotericin B injections on an outpatient basis 3 times/week. This regimen was continued for a further 3 months at which point the lesions appeared stable. All medications were then stopped and the patient was followed with approximately monthly brain MRI scans. Two months after stopping treatment, brain MRI showed that the left frontal abscess was enlarging again and had not responded to treatment. At this point, the patient was re-admitted to the hospital and a bifrontal craniotomy was performed for internal debridement of the left-side brain abscess, with removal of the right-side Ommaya reservoir and replacement of only the left-sided Ommaya reservoir. At that time, analysis of intraoperative specimens showed septated hyphae on smear and C. Bantiana on cultures. The dose of intracavitary amphotericin treatment was then increased to 1 mg every other day. After 1 week in the hospital, he was discharged home on oral voriconazole and intracavitary aspiration and amphotericin B instillation 3 times/week in the clinic. Later, he was transitioned to weekly aspiration/injections that were continued for another 3 months, during which findings on periodic MRI remained stable [Figure 3].

From the last surgical debridement onward, analysis of aspirated material from the persistent left-side lesion continued to show septate hyphae on smear with no fungal growth on culture. Then, in September 2014 (13 months after beginning intracavitary therapy), analysis finally showed no fungal elements on smear and no growth on
culture [Table 1]. From then, all anti-fungal treatments were stopped. At the time of writing this article, over 3 years from initial diagnosis, the patient remains off all antifungals and no longer receives intracavitary treatment [Figure 4]. He remains fully functional and socially appropriate with a normal neurologic exam and normal activity and interests. Although MRI scans continue to show ring enhancing lesions, they appear stable or slightly smaller on serial scans. We continue to monitor him with 6 monthly MRI scan.

**DISCUSSION**

Central nervous system infection with *C. bantiana* is a rare and often fatal infection. The mortality rate of this condition is more than 70%, despite aggressive multimodal therapy. Infection with this neurotropic fungus presents most commonly as brain abscess or rarely as meningitis. Predisposing factors are not well established, and while some reports implicate steroids and immunosuppressant use after solid organ transplantation, the majority of cases occur in immunocompetent patients. The fungus is widely disseminated in the environment, and the mode of entry is only vaguely understood. Revankar et al. suggested entry through inhalation of spores followed by hematogenous dissemination to the brain.

There are no clear guidelines regarding the treatment of this disease because of its rarity and lack of prospective trials. Treatments might include systemic antifungal therapy, burr-hole aspirations, open internal surgical debridement, wide extracapsular surgical resection, and rarely intrathecal/intracavitary therapy. Systemic antifungal monotherapy might be effective initially, but almost always leads to treatment failure from resistance and difficult antifungal penetration of the capsule of the abscess. Amphotericin B is the most commonly used antifungal agent. However, studies have shown less than minimum inhibitory concentrations of amphotericin B in the cerebrospinal fluid and brain parenchyma after systemic administration of standard doses (70 mg/day). Newer antifungals, such as voriconazole and posaconazole, appear to

| Date     | Smear                  | Culture                          |
|----------|------------------------|----------------------------------|
| 4/23/13  | Septate hyphae         | *Cladophialophora bantiana*      |
| 4/28/13  | Septate hyphae         | *Cladophialophora bantiana*      |
| 5/8/13   | No fungal elements     | No growth                        |
| 10/18/13 | Septate hyphae         | *Cladophialophora bantiana*      |
| 11/22/13 | Septate hyphae         | No growth                        |
| 12/30/13 | Septate hyphae         | No growth                        |
| 1/13/14  | No fungal elements     | No growth                        |
| 1/20/14  | No fungal elements     | *Penicillium* and *Cladosporium*|
| 2/18/14  | Septate hyphae         | No growth                        |
| 3/24/14  | No fungal elements     | No growth                        |
| 5/2/14   | N/A                    | No growth                        |
| 6/25/14  | Septate hyphae         | No growth                        |
| 7/23/14  | Septate hyphae         | No growth                        |
| 9/5/14   | No fungal elements     | No growth                        |
| 9/17/14  | No fungal elements     | No growth                        |
| 9/24/14  | No fungal elements     | No growth                        |
| 10/15/14 | No fungal elements     | No growth                        |
| 10/29/14 | No fungal elements     | No growth                        |
have high efficacy, improved bioavailability, and are well tolerated.\[^{[2,1,13,16,29,35]}\] Alternatively, itraconazole was proposed if the patient does not respond to voriconazole.\[^{[38]}\] Antifungal therapy can be guided by susceptibility testing and clinical efficacy. Animal studies have shown that in vivo antifungal efficacy against C. bantiana is consistent with in vitro antifungal susceptibility.\[^{[12,27,31]}\] Despite these improved agents, failure with C. Bantiana continue to be reported.\[^{[21]}\]

Surgical management of this disease may include initial biopsy with aspiration, possibly followed by more aggressive excision once hyphae are identified. For lesions that are amenable to early wide surgical resection, this may be an important factor in achieving a possible cure and improved outcome.\[^{[38]}\] However, the role of surgical extracapsular resection is far from proven because many cases (9/24 reviewed here) that were similarly treated with excision did not survive.\[^{[41]}\] while at least one case treated only with aspiration and systemic amphotericin B made a good recovery. Furthermore, because of size and location, a wide resection may not be desirable or possible. Table 2 summarizes several cases\[^{[4,22,36,40,42,43]}\] in the literature that reported survival with C. bantiana brain abscess, and shows that each case was treated differently, adding to the existing uncertainty regarding the most appropriate treatment.

Prolonged intracavitary treatment has seldom been proposed for intracranial fungal abscesses and appears not to have been published for the specific treatment of C. bantiana.\[^{[1,9,10]}\] Intraventricular amphotericin treatment appears not to be well tolerated with significant side effects and potential for seeding the intraventricular space by passing a catheter.\[^{[1]}\]

In the case documented here by serial brain MRIs, surgical resection was almost always followed by worsening of the abscess, despite continued systemic anti-fungal therapy. This observation raises several questions. First, how wide a margin is necessary to eradicate fungal brain abscess in comparison to bacterial brain abscess? In bacterial brain abscess, neuropathological studies have shown that in the stages of late cerebritis, early and late capsular formation, no bacteria could be identified in the collagen capsule or the surrounding reactive gliosis zone.\[^{[9,30]}\] In contrast, fungal brain abscess showed diffuse infiltration of the brain parenchyma with fungal hyphae beyond the fibrous capsule. The adjacent brain parenchyma was reactive and hyperemic with granulomas containing fungi, necrotic debris, acute and chronic inflammatory cells, and multinucleated giant cells [Figure 5].\[^{[19]}\]

Second, if an additional resection margin is needed, is that margin compatible with preservation of function in the affected location? Third, what are the effects of pus spillage and piecemeal removal? While with resection of bacterial brain abscess close margined extracapsular removal is typically effective, and some pus spillage is not

| Reference      | Patient age, sex | Radiological findings                  | Treatment                                                                 | Outcome                        |
|----------------|------------------|----------------------------------------|---------------------------------------------------------------------------|--------------------------------|
| Banerjee et al.\[^{[9]}\] | 28y, M           | CT – Left frontal SOL                  | Total excision, systemic Amphotericin B                                    | Survived                       |
| Vyas et al.\[^{[43]}\]   | 35y, M           | CT – Left frontal lobe lesion          | Total excision, Systemic Fluconazole                                      | Survived on follow up for 5 years|
| Sood et al.\[^{[40]}\]    | 25y, M           | CT – Left posterior frontal lesion     | Total excision, systemic Fluconazole                                      | Survived                       |
| Raut et al.\[^{[30]}\]    | 26y, F           | CT – Left frontoparietal ring-enhancing lesion | Stereotactic aspiration, 2 weeks later – total excision of capsulated lesion, amphotericin B (systemic and intrathecal) | Survived on follow up for 2 years, neurological deficit unchanged |
| Velho et al.\[^{[42]}\]   | 40y, M           | CT/MRI – Multiple ring-enhancing lesions in right frontoparietal region | Subtotal excision, systemic Fluconazole, Follow up scan at 4 weeks - increase in abscess size - total excision | Survived on regular follow up |
| Lakshmi et al.\[^{[22]}\] | 23y, M           | CT – Ring-enhancing lesion in Lt capsuloganglionic region | Burr hole aspiration, systemic amphotericin B                             | Survived, Good cure            |

**Figure 5:** Resected cyst wall (hematoxylin and eosin; magnification, ×100) showing granulomatous inflammation with necrosis and reactive changes (a) and septated branching hyphae with oval conidia (b). Gomori methenamines Silver stain (GMS, ×100) of the tissue block in a showing the fungal elements (c).
We used an initial intracavitary therapy. Further experience with future cases will be needed to verify these impressions.

Prolonged follow-up (>1 year) is essential because late relapses are reported to be possible. Successful treatment courses have been as short as 3 months and lasted more than a year. Therapy should not be stopped until complete radiographic resolution occurs or there is evidence of halted progression on repeat MRIs spanning a prolonged period of time. In our case, the length of treatment was guided by the gradually negative aspirate cultures and disappearance of fungal elements in the aspirate. Once these normalized, we did not attempt to resect the persistent enhancing capsule of the lesions because the patient was already asymptomatic and we feared reactivation of possible dormant residual elements by the surgery. At this writing, the patient has been followed for over 3 years without clinical or imaging evidence of reactivation. Remarkably, the patient remains neurologically normal and active.

Based on these observations, our current treatment paradigm for black mold fungal brain abscess is to first make a diagnosis by stereotactic aspiration, and if black mold is found, attempt as wide a surgical resection as possible, followed by treatment with maximal systemic medical therapy as tolerated with voriconazole and amphotericin. If the lesion shows early recurrence, rather than attempting further resection of the capsule, consider internal debridement leaving the capsule intact and place a catheter with Ommaya reservoir for intracavitary antifungal therapy. This strategy accepts that the capsule may be important to the patient’s immune defense against the fungus and helping that defense barrier with intracapsular and systemic antifungal agents rather than capsular removal may be the better strategy for that patient. If this strategy is adopted, long-term regular treatment on an outpatient basis should be anticipated. Imaging showing persistence of the capsule should not be considered a treatment failure as long as further progression is not obvious. Aspiration and antifungal instillation should continue until the aspirate is cleared of fungal elements and the cultures turn persistently negative. Patience can pay off with eventual sterilization in situ of the lesion with good clinical outcome, despite imaging persistence of the lesion.

CONCLUSION

Optimal surgical treatment of fungal brain abscess may differ from that of bacterial brain abscess. In particular, the role of extracapsular surgical excision may not be as effective for fungal brain abscess as for bacterial abscess. While bacteria are confined by the fibrous capsule, fungal hyphae can extend beyond it. In addition, antibiotics for bacteria may be more effective than those for fungi. In cases where surgical resection of fungal brain abscess is followed by early enlargement or rapid recurrence, or the sensitive location does not allow initial wide resection, long-term repeated aspiration with intracavitary amphotericin B together with systemic oral voriconazole may still prove successful.

DISCLOSURE

We have read and understood SNI policy on declaration of interests and declare that we have no competing interests.

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Conflicts of interest
There are no conflicts of interest.

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