Cerebral phaeohyphomycosis—a cure at what lengths?

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Cerebral phaeohyphomycosis is a fungal infection of the brain typically caused by *Cladophialophora bantiana*, *Exophiala dermatitidis*, and *Rhinocladiella mackenziei*, all of which belong to the order Chaetothyriales. The disease results in black, necrotic brain tissue, black pus, and black cerebrospinal fluid. Pathogens usually reach the brain through the bloodstream or lymphatic fluid and occasionally through direct spreading or accidental inoculation. Patients can present with hemiparesis, tonic spasm, headache, fever, sensory variation, cerebral irritation, and even psychotic behavioural changes. Radiological images are characterised by ring-enhanced signs and hyperdense and hypodense lesions. Pathological features frequently include black-to-brown necrotic tissue or dark-coloured pus, granulomatous inflammation, giant cell vasculitis, and pigmented fungal elements, which are easily seen on a direct potassium hydroxide smear, a rapid method for diagnosis. Black fungi can be cultured from a biopsy specimen. Combined antifungal chemotherapy, surgical debridement, and careful immunological interventions are strongly recommended to eradicate these intractable infections.

Introduction

Cerebral phaeohyphomycosis is the collective name for a group of cerebral fungal infections that are characterised by black necrotic tissue, black pus, and black cerebrospinal fluid (CSF).[1–3] If untreated, the infection leads to death within weeks, months, or, occasionally, years.[1–6] This infection is caused by a group of black fungi, and emerging pathogens from this group are still being encountered.[5–12] Most of the pathogens belong to a single order of environmental fungi, Chaetothyriales, according to new genetic studies.[1]

	Order	Number of cases
Neofusicoccum mangiferae	Botryosphaeriales	1
Cladophialophora bantiana	Chaetothyriales	>78
Exophiala asiatica	Chaetothyriales	1
Exophiala dermatitidis	Chaetothyriales	>25
Exophiala jeanselmei	Chaetothyriales	1
Fonsecaea monophora	Chaetothyriales	2
Fonsecaea pedrosoi	Chaetothyriales	1
Rhinocladiella mackenziei	Chaetothyriales	21
Neoscytalidium dimidiatum	Helotiales	3
Acrophialophora fusispora	Incertae sedis	1
Ochroconis gallopavum	Incertae sedis	4
Bipolaris hawaiiensis	Pleosporales	2
Bipolaris spicifera	Pleosporales	2
Bipolaris sp	Pleosporales	1
Curvularia lunata	Pleosporales	4
Curvularia pallescens	Pleosporales	1
Dissitimurus exedrus	Pleosporales	1
Exserohilum rostratum	Pleosporales	1
Chaetomium atrobrunneum	Sordariales	3
Chaetomium globosum	Sordariales	1
Chaetomium perlucidum	Sordariales	1
Chaetomium strumarium	Sordariales	2
Phialemonium obovatum	Sordariales	1
Nodulisporium sp	Xylariales	1

Table: **Aetiological agents of cerebral phaeohyphomycosis**

The sporadic and non-random distribution of these infections often leads them to be thought of as isolated events. Thus far, the infection has only been diagnosed after the pathogenic agent has been cultured from biopsy specimens, which delays treatment and results in high mortality.[13–25] Early diagnosis and effective therapy would improve patients' outcomes, but these depend largely on doctors' full understanding of the disease. This Review will focus on clinical signs and symptoms, radiographical features, pathology, diagnosis, and treatment, in addition to the aetiology, epidemiology, and risk factors of this infection.

Aetiology and epidemiology

By the year 2000, 106 orders of fungi were recognised; 396 species in 25 orders were associated with infections in mammals, and more than 20 species were associated with systemic or disseminated human infection.[1] As already mentioned, most of the causal agents of cerebral phaeohyphomycosis belong to a single order of environmental fungi, Chaetothyriales, but a few are distributed in the orders Pleosporales, Sordariales, Xylariales, Helotiales, and Botryosphaeriales (table). This group of fungi are melanised whether grown in vivo or in vitro, and they grow slowly and restrictedly.[1] Chaetothyriales includes several pathogens that can cause a disseminated fatal infection as well as a wide array of species that are involved in pulmonary, subcutaneous, and cutaneous infections. Three species of Chaetothyriales are primarily involved in brain infection: *Cladophialophora bantiana*, *Exophiala dermatitidis*, and *Rhinocladiella mackenziei*.[5,6,11,26–29] Although emerging pathogens are still being identified (table),[30–40] this article focuses on the three primary species.[7–12]

C bantiana—previously known as *Cladosporium trichoides*, *Cladosporium bantianum*, and *Xylohypha emmonsi*—is the most frequently isolated pathogen from cases of cerebral phaeohyphomycosis; more than 70 cases of infection with this organism have been published.[5,13,15–18,21–25,28,41] The pathogen is distributed worldwide, although infections are most common in

subtropical, non-arid climate zones.[5,28] Diagnosis depends largely on clinical disease recognition and pathogen identification.[19,22,23,42,43]

E dermatitidis has been known to cause brain infections in Japan since 1961, when it was called *Wangiella dermatitidis*.[44] Additional cases have been described from Japan, China, Korea, Pakistan, and Singapore.[20,28,45–49] Because most fatal brain infections were observed in young Asians with no history of immune disorder, *E dermatitidis* infection was previously assumed to be race-dependent.[5] However, more recent cases have included five cases of cerebral meningitis associated with steroid injections contaminated with *E dermatitidis* in the USA and 19 patients with *Exophiala jeanselmei* fungaemia (three of whom died because they did not receive therapy before culture results were known) associated with contaminated deionised water from a hospital pharmacy in Brazil. Consequently, cerebral phaeohyphomycosis is now believed to be a disease to which all people are susceptible.[45,50–52]

R mackenziei,[29] previously known as *Ramichloridium mackenziei* and *Ramichloridium schulzeri*, is a recently recognised endemic pathogen that causes cerebral phaeohyphomycosis.[53–57] Infections with this pathogen have all been reported in patients living in or originating from the Middle East—a hot, dry region. *R mackenziei* is the only neurotropic fungus that has been reported from this region.[2,13,14,26,28,53–61]

Risk factors

Roughly half of patients with cerebral phaeohyphomycosis are otherwise healthy individuals, often in young men.[5,6,45] Infections have also been reported in patients receiving solid-organ transplants, with chronic organ failure, with primary or secondary immune-system disorders, with malignant diseases, with other infections, or patients who are on steroid therapy.[6,16,62] Among 54 patients with *C bantiana* infection, 21 were otherwise immunocompetent, five had an uncertain immune function, and ten cases were secondary to an infection with bacteria, parasites, or other fungi such as cryptococcus.[5] The remaining patients had chronic organ failure, had undergone organ transplantation or other surgery, or were on steroid therapy. In a review of 101 patients with cerebral fungal infections, 53 were immunocompetent and 29 had immune dysfunction (18 patients had received organ transplantations, ten had malignant diseases, and one had AIDS). Five patients were on steroid therapy, four were drug users, three had organ failure, one had diabetes, and six had trauma (one was trauma to the eye, two were trauma to the head, one was head surgery, one was from spinal acupuncture, and one was trauma at an unlcear site).[6] Among 25 patients described from 1999 to 2004, infection was associated with contaminated medication in five, organ transplantation in five, chronic organ failure in three, malignant disorders in three, primary immunodeficiency in one, AIDS in one, and chronic diseases in two; five had no prior disease.[28,50] Of the 20 patients that have been described since 2004, ten were immunocompetent, four had had organ transplantations, two had primary immunodeficiency, and four had chronic diseases.[13–25]

Pathways to the brain

Chaetothyriales can reach the brain through blood or lymphatic vessels, by directly spreading from adjacent lesions, or by accidental inoculation.[6,7,50] Primarily, the fungi disseminate to the CNS through blood vessels; fungal elements have been frequently seen in arterial walls.[17,23,24,43,63] Because many patients have a pulmonary infection with the same agent before or at the same time as the cerebral infection, the potential for pulmonary entry has been hypothesised and confirmed in animals.[1,52,55,63–65] Exposure to soil or plant matter may be the source of respiratory infection.[20,23,52] The multiple brain abscesses that are commonly seen might also suggest dissemination through the bloodstream. Skin or pharyngeal trauma has also been suggested as a portal of entry.[19,20,22,23,52,66]

Secondarily, the fungus might reach the brain through lymphatic vessels. Cervical lymph node infection has often been reported before a cerebral infection that follows an event such as childbirth. Fungal elements have also been observed in lymphatic vessels.[20,44,46]

In some cases, the fungus infects the CNS by directly spreading from adjacent organs, such as the sinus and orbit.[19,20] Accidental inoculation has also been reported after an epidural injection with a contaminated steroid solution and through an open cranial wound.[50,67,68] These inoculations have allowed the mean incubation period to be calculated: about 1–3 months from inoculation to development of overt cerebral infection.[50,67,68]

Why the fungus has an affinity for brain tissues is unknown. An intriguing possibility is that melanin, which has been investigated as a toxic factor, may be responsible for CNS localisation.[66,69,70] Malignant melanoma has similarly high rates of CNS metastasis, more than 40% in an autopsy series.[71] Disrupting the polyketide synthase gene *WdPKS1* in *E dermatitidis* produces a melanin-deficient phenotype that is less virulent and more easily killed.[70]

Clinical presentation

Clinical presentation of cerebral phaeohyphomycosis is typical of what would be expected with any brain lesion, including symptoms and signs such as seizures,[17] headache,[17] cerebral irritation, fever, and psychotic behavioural changes, although hemiparesis and hemisensory loss are the most common symptoms. Limb weakness is a common presenting symptom.[2,13,17,21,60,65,72–77] Unilateral hemisensory loss and paralysis may make cerebral phaeohyphomycosis seem more like a stroke or tumour, but because it is an infection, the disease usually

occurs concurrently with fever, headache, and other symptoms of infection. These symptoms are needed to differentiate the infection from other disorders with similar clinical manifestations. Symptoms like those of the common cold often appear at the beginning of infection, and as the disease progresses, other toxic symptoms might develop, such as fever with chills in the event of a comorbid bacterial infection.[8,50,78]

If the cranial nerve is involved, focal neurological deficits such as diplopia, vision loss, eyeball fixation, dysarthria, and ataxia would manifest.[8,19,23,42,46,59,79] Tonic spasm, chronic convulsion, atonic spasm, and focal motor seizures result from cerebral cell degeneration and necrosis.[15,17,59,60,78,80–82] Sometimes seizure is the first symptom, which can easily lead to misdiagnosis.[17,82,83]

Headache affects 55% of patients.[6] If headaches were caused by obstructive hydrocephalus, the pain would be extremely severe, similar to that of meningitis, but examination of CSF would show negative results, with the exception of expiratory changes in CSF pressure.[42,46,48,75]

Meningeal irritation could be a sign of cerebral phaeohyphomycosis, even in the absence of primary cerebrospinal meningeal infection. Most patients who had symptoms of meningitis, such as neck stiffness, did not show meningeal involvement in histopathology. The most likely reason for this finding is that brain tissue oedema increases the pressure of CSF, which causes meningeal signs.[16,22,41] Primary meningeal infection would most likely discolour CSF, or turn it black, and be accompanied by typical symptoms of headache, vomiting, stiffness, and papilloedema.[15,20,47,50,55] Chronic basal meningitis might result from mycotic aneurysm of the arteries.[23]

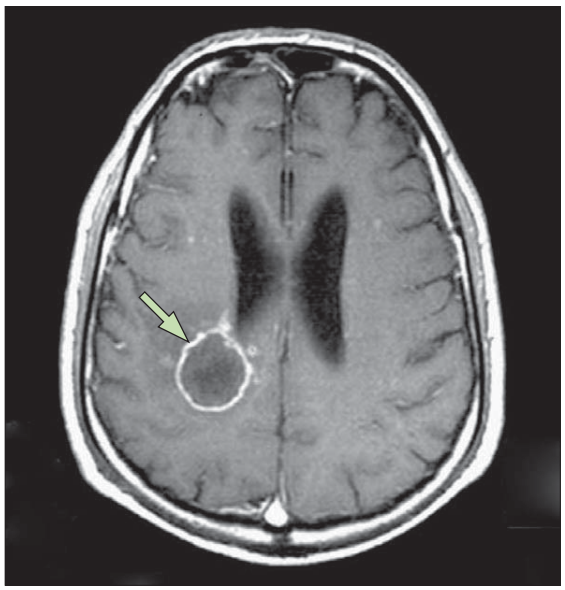

Figure 1: **MRI showing ring-enhancing lesion in the right hemisphere of a brain infected with *Rhinocladiella mackenziei***
Reproduced with permission from Elsevier Health.[61]

Lymphadenovarix (a varicose deformity of lymph nodes) with fever is another common sign before brain infection, primarily involving the cervical node. It appears months to years before the fungus moves into the brain, after which it spreads rapidly and is fatal in a matter of days.[5,20,46]

Concomitant symptoms depend on which other organs are involved. Respiratory infection with cough and sputum develops before or at the same time as brain infection in many patients.[22,23,66] Stomach ache, jaundice, hiccup, dark brown urine, liver dysfunction, and splenitis have all been recorded in patients with cerebral phaeohyphomycosis.[61,79]

CSF discolouration is a unique characteristic if the cerebrospinal membrane is involved; CSF appears black in *Exophiala* spp infection, green to brown in *R mackenziei* infection, and yellow-brown in *C bantiana* infection.[20,42,43,47,50] If the infection does not invade the cerebrospinal membrane, CSF test results are usually abnormal with hypoglycorrhachia, slight increases in protein concentration, and sometimes pleocytosis with eosinophils in addition to peripheral blood eosinophilia.[43,48]

Radiological features

In most infections in immunocompetent patients, only a single lesion was seen; most patients with multiple lesions were immunocompromised.[13–15,21,23,25,73,74,81,84–87] In CT examinations, the typical finding is a ring-enhancing lesion with a low-attenuation core surrounded by hypodense lesions (figure 1).[13,15,17,19,22,24,44,74,79,80,83,88,89] MRI in *C bantiana* and *R mackenziei* infections reveals ring-enhancing lesions on T1-weighted images, hypointensity of the ring on T2-weighted images, and low-to-high signal intensity on diffusion-weighted imaging. The low attenuation core suggests the presence of necrotic tissue or pus, whereas the ring-enhancing sign usually represents a granulomatous lesion that is quite different from images of bacterial or parasitic infections, which typically manifest as multifocal, hypodense, non-enhancing lesions.[83,88–90]

In the early stages of infection, decreased attenuation can be seen in the highly attenuated zone of infected areas, which often leads to misdiagnosis as a brain tumour.[23,48] A typical ring-enhancing, hypodense lesion would appear as the infection progressed.[8,21,44,48,60,78] Irregular, variably contrast-enhancing masses can resemble either metastasis or high-grade glioma.[42,43,91]

Pathological characteristics

On operation or autopsy, infected areas commonly appear, as with the CSF, as brown-to-black lesions in *Exophiala* spp infection, yellowish-brown in *C bantiana*, and dark greenish-brown in *R mackenziei*. Typically the abscess cavity has a thick wall filled with non-foul-smelling pus surrounded by hyperplastic tissue.[8,54–56,79,92,93]

Three major features might be observed under a microscope: granulomatous inflammation, dematiaceous

fungal material, and vasculitis with giant-cell infiltration. Granulomatous inflammation is the main histological feature, and it is usually characterised by the presence of multinucleated giant cells, histiocytes, lymphocytes, neutrophils, and necrotic debris with dematiaceous fungal materials (figure 2).[8,9,15,17,26,46,63,74,75,94–97]

Pigmented fungal elements must be found to conclusively diagnose cerebral phaeohyphomycosis. On a haematoxylin and eosin stain, these would be seen as dark-walled, branched, and septate hyphae, with possibly other forms of pseudohyphae, conidia, or budding cells, which would be stained intensely with Periodic acid-Schiff, Grocott's methenamine silver, or Congo red stain (figure 2).[8,17,19,21,63,76,80,92,98,99] Sometimes fungal elements can be seen inside the multinucleated giant cells.[8,9,75,94]

Vasculitis with giant-cell infiltration is an important characteristic in this infection, usually with mycotic thrombosis and subsequent artery infarction. Aneurysm occasionally occurs if the artery wall is destroyed.[17,23] Sometimes fungal stroke followed by mycotic thrombosis, aneurysm, or haemorrhage is the presenting sign that needs to be differentiated from a regular stroke.[8,9,42,44–46,63,94,100]

Diagnosis

With typical clinical features and characteristic radiographical images, diagnosis is easy. However, pigmented hyphae and other fungal elements must be present to confirm the infection. Direct smear examination with potassium hydroxide is a rapid way to confirm the diagnosis, but examining a frozen section of the specimen is an alternative.[101] Black fungus can be recovered from the pus, brain-biopsy tissue, CSF, or blood when the specimen is inoculated on a culture medium like Sabouraud dextrose agar, malt extract agar, and potato dextrose agar and incubated at 27°C and 37°C.[1] Colonies vary in colour from dark green or brown to black.[1] Aetiological identity can be confirmed in reference laboratories.

Although CT-guided stereotactic needle aspiration is a less invasive biopsy method, burr-hole tapping can be therapeutic (by draining pus) and provide biopsy specimens.[2,21,25,74,102,103] Lumbar puncture is helpful to examine CSF for factors that indicate meningitis if the cerebrospinal membrane is involved. Differential diagnoses include brain tumour, stroke, tuberculosis, and parasitic and other infections.[42,58,93,104]

Treatment

Treatments include surgical debridement, combined antifungal therapy, and immune enhancement, although an isolated lesion can be removed successfully without chemotherapy.[13,65,105,106]

Antifungal agents

Antifungal therapy should be combined with monitoring of antifungal susceptibility and clinical efficacy. Experiments on animals have shown that the in vivo antifungal efficacy against *Cladophialophora bantiana* is consistent with in vitro antifungal susceptibility.[13,107] Three combinations are suggested: terbinafine plus an azole; an echinocandin (caspofungin, micafungin, and anidulafungin) plus amphotericin B or an azole; and flucytosine

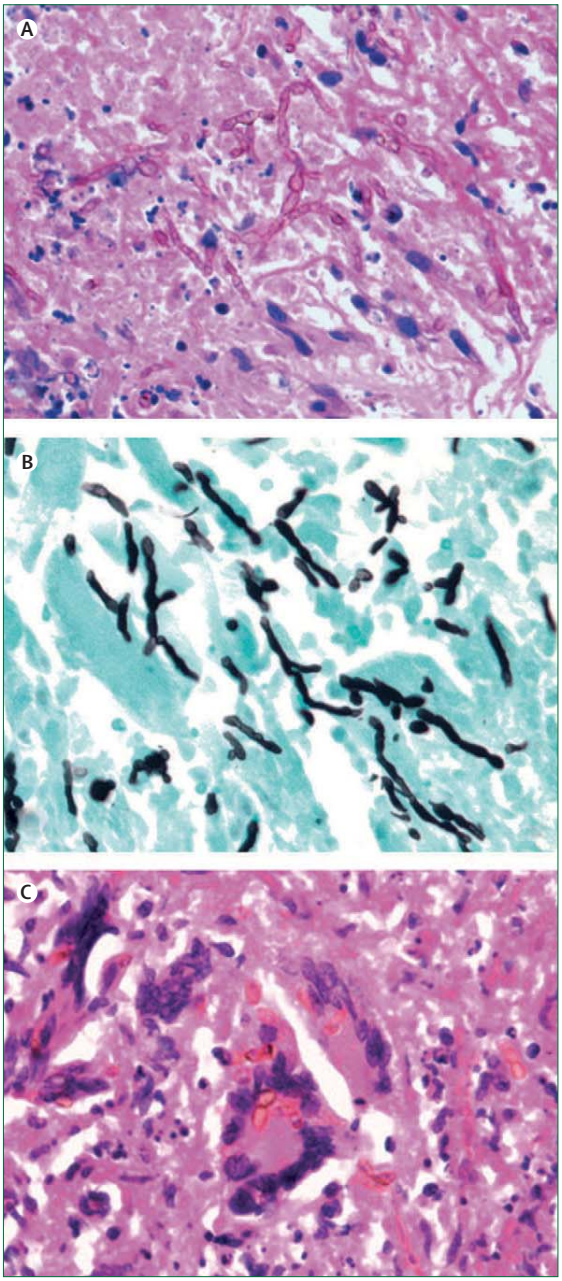

Figure 2: **Histopathological features of *Cladophialophora bantiana***
Pigmented fungal hyphae (A), elongated, and septate with unicellular lemon-shaped conidia (haematoxylin and eosin stain). The fungal elements (B) are intensely positive with Grocott's methenamine silver. Hyphae and conidia shown inside multinucleated giant cell (C), and in the surrounding brain parenchyma (hematoxylin and eosin stain). Magnification ×220. Reproduced with permission from Wolters Kluwer Health.[17]

with combinations of amphotericin B, itraconazole or posaconazole, or an echinocandin (these agents could enhance intracellular penetration and subsequent activity of flucytosine).[13,83] Nearly all successfully treated cases were treated with combination therapy;[13,52] monotherapy might seem effective initially, but it almost always results in treatment failure.[2,3,8,11,13,21,50,52,60] As new antifungal drugs like voriconazole and posaconazole become available, however, monotherapy may become more successful, because they have high efficacy, improved bioavailability, and are well tolerated.[13,15,105,106,108–110]

As high minimum inhibitory concentrations often result in treatment failure,[19,107,110] antifungal susceptibility should be monitored at the beginning and during the course of therapy because of the risk of resistance and cross-resistance induced by contact with antifungal drugs.[108,111,112] Alternating drugs might help avoid the development of resistance because long-term exposure to a particular regimen can induce resistance.[80,113] Regardless of in vitro susceptibility results, clinical and radiological improvement, which usually appears within a week or two of initiating treatment, is the best sign of clinical efficacy.[13,86]

Side-effects must be taken into account so that the treatment does not kill the patient before the fungus does.[13,109] Some antifungal agents, especially amphotericin B, are highly potent and can cause hypokalaemia, nephrotoxity, and hepatotoxity, any of which can be fatal.[6,7,21,41] However, long-term triazole therapy was reasonably safe in multiple studies and animal experiments.[13]

The duration of treatment necessary to eradicate the infection varies according to multiple factors, including the cause of disease, whether surgical intervention was necessary, and patient's immune status. Successful treatment courses have been as short as 3 months and lasted more than a year. Therapy should not be stopped until complete radiographical resolution occurs.[15,21,76,81]

Surgical debridement

Surgical debridement of lesions is crucial in managing the infection. Debridement can greatly decrease the amount of fungal material at an infected site, and if the infection is small and localised, it can even be completely removed with a margin of adjacent, healthy tissue.[17,24,52,114] As brain abscesses form, pus must be drained because the thick wall around the abscess prevents drugs from penetrating. Burr-hole tapping and excision are surgical options.[76] Sometimes craniotomy must be done to excise a persistent abscess that resists antifungal drugs and repeated tapping. Meticulous care must be taken in the surgical procedure to prevent reinoculation of the fungus, which would lead to the recurrence and spread of the infection.[15,19,52,59,83]

Immunotherapy

Immunological intervention might be needed for patients with intractable infections. For those who are not immunocompromised, interferons, interleukins, transfused leucocytes, and colony-stimulating factors might enhance immunity by directly stimulating the immune system and might be useful as adjunct therapy.[52,115–118] In patients with compromised immune systems due to organ transplant, malignancy, or other factors, immune-suppressing drugs might need to be adjusted to fight fungal infections, carefully balancing aggressive antifungal treatment with the original therapy (antirejection drugs, chemotherapy).[52,74] Interferons, such as interferon γ, a protein produced in response to infections, might be a powerful weapon in the battle against fungal infections in immunocompromised patients.[119]

Prognosis

Mortality for cerebral phaeohyphomycosis can be as high as 100% without treatment. For those who are treated with surgery and chemotherapy, mortality is still about 65%.[13,14] Matsumoto[98] reviewed 21 cases of systemic *Exophiala* spp infections and mortality was 48%, and the infection had a notable tendency to invade the CNS. In a review of ten culture-proven *C bantiana* infections, mortality was 50% after patients underwent surgery that was followed by combination antifungal therapy. Of the 20 infections reported since 2004, only five patients survived.[13–25,117–119]

Conclusions

Although cerebral phaeohyphomycosis has been recognised for decades, the infection is still poorly understood and is easily overlooked. The mortality rate of this disease remains high. Cerebral phaeohyphomycosis should be suspected in a patient who presents with hemiparesis, tonic spasm, or sensory variation, or all of these symptoms, and with symptoms of infection such as headache, fever, and fatigue. If a ring-enhancing lesion is seen on CT images, CT-guided stereotactic needle aspiration is strongly recommended to produce a biopsy specimen for potassium hydroxide examination, cultivation, and histopathology. Giant-cell vasculitis or granulomatous inflammation suggests the infection, and pigmented hyphae or conidia confirm the diagnosis. The aetiological agent can be identified by culture. Treatment

Search strategy and selection criteria

We searched Medline for English-language manuscripts limited to "human" and "case reports", "letters", "reviews" and "clinical conferences" from 1966 to 2008. We used MeSH terms "mycoses", "phaeohyphomycosis", or "chromoblastomycosis", in combination with MeSH term "brain" for brain fungal infections. The results were combined with "Exophiala" (MeSH), "Cladosporium" (MeSH) or its synonyms "Cladophialophora" or "Xylohypha", "Rhinocladiella" or its synonym "Ramichloridium", respectively.

should begin as soon as possible and might require antifungal chemotherapy, surgical debridement, and immunological intervention. Cerebral phaeohyphomycosis can be cured with early diagnosis and aggressive therapy.

Conflicts of interest
We declare that we have no conflicts of interest.

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