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Fonsecaea monophora cerebral phaeohyphomycosis: case report of successful surgical excision and voriconazole treatment and review

SOPHIA KOO*†‡, MICHAEL KLOMPAS*‡§ & FRANCISCO M. MARTY*†‡

**Division of Infectious Diseases, Brigham and Women's Hospital, †Dana-Farber Cancer Institute, ‡Harvard Medical School, and §Harvard Pilgrim Health Care Institute, Massachusetts, USA*

We report a case of *Fonsecaea monophora* cerebral phaeohyphomycosis successfully treated with surgical excision and voriconazole monotherapy in a patient receiving maintenance immunosuppression therapy for 8 years after cadaveric renal transplantation. She presented with a severe frontal headache in the absence of any constitutional or neurologic symptoms. Brain magnetic resonance imaging showed an irregular 3.1 × 3.4 cm ring-enhancing lesion in her left frontal lobe. The patient underwent craniotomy and resection of her mass, with intraoperative spillage of some of her abscess contents into her lateral ventricle. Histopathology of her resected mass showed necrotic fragments of brain parenchyma with granulomatous inflammation and numerous pigmented fungal forms. A mold, recovered from cultures inoculated with portions of her brain resection specimen, was later definitively identified as *Fonsecaea monophora*. Initial serum (1→3) β-D-glucan (BG) levels exceeded 500 pg/ml. The patient received voriconazole, which she tolerated well, without recurrent headaches or abscess formation noted on serial brain imaging. Her BG declined to <31 pg/ml one year following her abscess resection. She discontinued antifungal therapy after an 18-month treatment course, and has remained free of any clinical or radiographic evidence of recurrent abscess formation three years later.

Keywords *Fonsecaea monophora*, cerebral phaeohyphomycosis, beta-glucan, voriconazole

Introduction

Cerebral phaeohyphomycosis is an uncommon central nervous system infection caused by neurotropic dematiaceous fungi [1,2]. Members of the order *Chaetothyriales*, i.e., *Cladophialophora bantiana*, *Rhinocladiella mackenziei*, and *Exophiala (Wangiella) dermatitidis* account for the vast majority of reported cases, but other members of this order and other non-cryptococcal melanized fungal species have also been sporadically implicated in human neuroinvasive disease [1,3,4]. These infections often affect patients without discernible immune deficiencies or other predisposing conditions, and are frequently fatal despite appropriate antifungal therapy and surgical excision [1–3]. A comprehensive review of reported cerebral phaeohyphomycosis cases in the era prior to routine use azole antifungals indicated 86% mortality when aspiration or partial excision alone was used in treatment, 62% mortality with complete surgical excision, and 70% mortality when a combination of either aspiration or excision and systemic antifungal chemotherapy was employed [3].

The taxonomy of the *Chaetothyriales* genus *Fonsecaea* was revised in 2004 to include two separate species, *F. monophora* and *F. pedrosoi*, based on differences in their nuclear ribosomal internal transcribed spacer sequences and ribosomal DNA restriction fragment length

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Correspondence: Sophia Koo, MD, Division of Infectious Diseases, Brigham and Women's Hospital, 75 Francis Street, PBB-A4, Boston, MA 02115, USA. Tel: +1 617 525 8418; fax: +1 617 732 6829; E-mail: skoo@partners.org

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polymorphism profiles [5,6]. While both species are agents of chromoblastomycosis, only *F. monophora* has been implicated in neuroinvasive disease [5,6]. *Fonsecaea monophora* cerebral phaeohyphomycosis is an extremely rare entity – only two cases have been formally reported in the literature to date [7,8] – and management of these cases remains largely undefined.

Case report

A 48-year-old female renal transplant recipient was hospitalized due to progressively severe frontal headaches of two weeks duration. She described the headache as sharp, constant, and radiating from her frontal regions to the back of her head. She noted discomfort and stiffness of her neck muscles and mild photophobia. She took several doses of acetaminophen without relief of her headache. She had a long history of migraine headaches and intermittent vertigo, but felt that her recent headaches were distinct in character and far more severe than her previous headaches. She denied any fevers, chills, sweats, weight changes, weakness, numbness, tingling, speech difficulties, gait difficulties, vertigo, dizziness, or visual changes.

The patient had undergone cadaveric renal transplantation eight years earlier for end-stage renal disease due to IgA nephropathy and chronic hypertension. She was receiving maintenance immunosuppression with prednisone 5 mg daily, tacrolimus 4 mg twice daily, and mycophenolate mofetil 250 mg twice daily. Her post-transplantation course was notable for two episodes of acute rejection, one week and six years after her transplantation, and cytomegalovirus reactivation three months post-transplant. She had numerous *Escherichia coli* urinary tract infections, some complicated by pyelonephritis and urosepsis, several vaginal condylomata, and grade II vulvar intraepithelial neoplasia. She was receiving trimethoprim-sulfamethoxazole prophylaxis for suppression of her frequent urinary tract infections.

She was born and raised in Jamaica, and emigrated to the United States approximately 20 years prior to her admission. She lived alone and had no pets or animal exposures. She previously worked as a bank teller. She denied any prior smoking or recreational drug use.

On presentation, her temperature was 37.0°C, heart rate 76 beats per minute, and blood pressure 141/97 mmHg. She appeared to be in mild discomfort because of her headache, but was fully awake and alert. Her neck was supple, with mild tenderness to palpation in her posterior neck muscles. Her fundoscopic, cranial nerve, motor, sensory, and reflex examinations were unremarkable. She had no skin lesions.

Her laboratory data was notable for 4,500 leukocytes/μl with 57.8% neutrophils, 35.1% lymphocytes, 6% monocytes, 0.7% eosinophils, and 0.5% basophils, hemoglobin of 9.2 g/dl, and 242,000 platelets/μl. Her renal function parameters were within her recent baseline range, with a blood urea nitrogen reading of 17 mg/dl and creatinine of 2.0 mg/dl. Her tacrolimus level was 5.3 ng/ml. Her erythrocyte sedimentation rate (ESR) was 46 and C-reactive protein (CRP) 1.2 mg/l.

A non-contrast computed tomogram (CT) demonstrated a hypodense 2.3×2.0 cm lesion in her left inferior frontal lobe with a thick, high-density rim (Fig. 1A). There was extensive edema involving the corpus callosum, causing mild subfalcine herniation. A subsequent brain magnetic resonance imaging (MRI) study showed an irregular 3.1×3.4 cm ring-enhancing lesion with extensive vasogenic edema and mass effect (Fig. 1B,C). There was an area of more solid-appearing enhancement in the lateral aspect of this lesion.

She underwent biopsy of her brain mass with a biopsy needle passed through a burr hole several times in an unsuccessful attempt to aspirate material from her lesion. On frontal craniotomy, she was noted to have a yellowish, avascular mass with a tough, fibrous capsule. Her mass had an area of central necrosis containing yellowish, purulent-appearing material. An initial Gram stain of this material showed no polymorphonuclear cells and no organisms. The encapsulated mass was fully resected, although some material from the central cavity did spill into her lateral ventricle. A frozen section of her lesion showed fibrotic tissue with numerous multinucleated giant cells, many containing budding yeast-like forms.

She received empirical liposomal amphotericin B 5mg/kg/day IV. Repeat CT imaging of her head showed a small area of hemorrhage in her operative bed, which remained stable on subsequent imaging during her hospitalization. A chest CT showed no infiltrates or nodules, and echocardiography was normal.

Final histopathology examination of sections of her frontal mass stained with hematoxylin and eosin (H&E) showed multiple fragments of brain parenchyma with marked necrosis, granulomatous inflammation, and innumerable melanized fungal forms with frequent fungal hyphae in foreign body giant cells (Fig. 2A), consistent with cerebral phaeohyphomycosis. A methenamine silver (MSS) stain showed abundant hyphae (Fig. 2B). Based on these findings, voriconazole 400 mg three times daily was added to her treatment regimen. She received a higher voriconazole dose than usual because of her concurrent use of phenytoin, a potent CYP3A4 inducer [9]. She received a brief tapering dexamethasone course postoperatively to reduce her cerebral edema, and her prophylactic phenytoin was switched to levetiracetam 500 mg twice daily to minimize drug interactions with voriconazole.

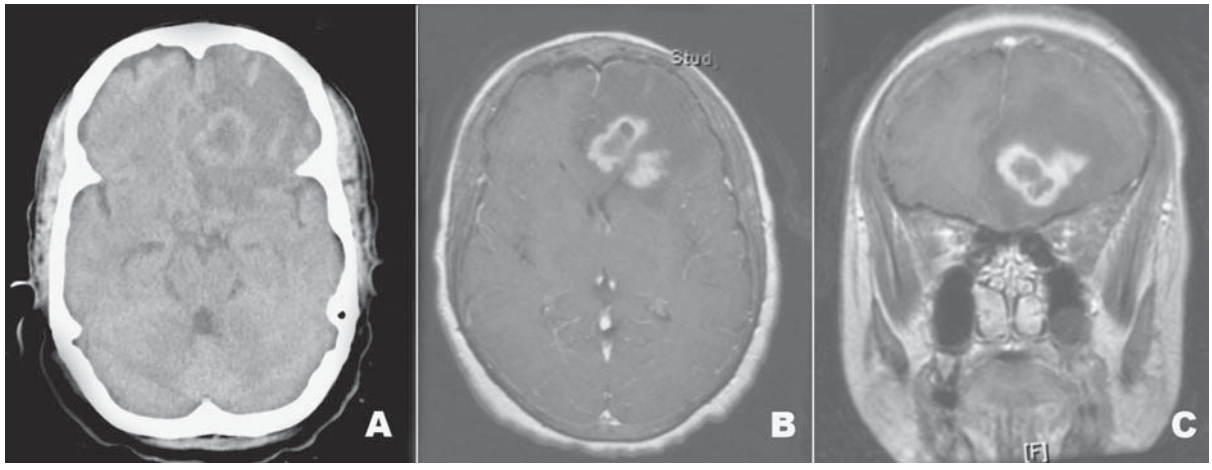

Fig. 1 Brain imaging on initial presentation: (A) Non-contrast CT image with left frontal lobe lesion with surrounding edema. (B, C) Axial and coronal MRI images demonstrating a ring-enhancing mass lesion associated with extensive vasogenic edema.

Sabouraud glucose agar cultures inoculated with portions of tissue from the patient's brain resection resulted in the growth of raised colonies of velvety, grayish-black mold. The colonies were slightly embedded in the agar and were black on reverse. On microscopy, mature hyphae appeared moderately dark and septate. Four types of conidial formations were observed that suggested *Fonsecaea* species: *Rhinocladiella*-like, *Cladosporium*-like, *Phialophora*-like, and thinner asterisk-like conidia directly arising from some hyphae. The isolate was sent to the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio for further identification and susceptibility testing. A few *Bacillus* species and coagulase-negative staphylococci were also found in the cultures but were presumed to be contaminants, and she she did not receive any specific therapy directed against these organisms. A serum (1→3) β-D-glucan (BG) sent the day following her surgery was greater than 500 pg/ml. One week later, her serum BG was 277 pg/ml.

The voriconazole dose was reduced to 400 mg twice daily after approximately one week, and she continued to receive daily liposomal amphotericin 5 mg/kg IV treatment for the remainder of her 2-week hospitalization. She recovered well from her surgery, and was discharged home with voriconazole 300 mg twice daily alone for treatment of her brain abscess.

The mold growing from her brain biopsy specimen was identified as *Fonsecaea monophora*, susceptible to liposomal amphotericin (minimum inhibitory concentration [MIC] 0.25 μg/ml), voriconazole (MIC 0.125 μg/ml), and posaconazole (MIC 0.03 μg/mL). Her isolate was sent to the Centraalbureau voor Schimmelcultures (CBS) Fungal Biodiversity Centre in Utrecht for definitive molecular identification. It was confirmed as *F. monophora* and deposited in the CBS culture collection as CBS 117542 [6].

Other than ongoing stable migraine headaches and a hospitalization for disseminated varicella zoster infection a year after her abscess resection, the patient recovered on voriconazole 300 mg twice daily. She had no visual disturbances, nausea, vomiting, hepatotoxicity, or QTc prolongation during her treatment course. Her steady-state serum voriconazole trough levels ranged from 0.65–1.71 μg/ml. Several serial follow-up MRI studies of her brain showed a stable left frontal lobe surgical cavity with residual surrounding T2 prolongation suggestive of postoperative gliosis. Her serum BG declined to 125 pg/ml at one month, 42 pg/ml at six months, and <31 pg/ml at one year following her abscess resection.

Voriconazole was discontinued in August 2006, 18 months after her initial presentation. She has done well clinically 3 years after the discontinuation of her voriconazole therapy, without any new headaches or neurologic symptoms. Serial brain MRI imaging has shown stable left frontal encephalomalacia and foci of magnetic susceptibility consistent with hemosiderin deposition at her prior abscess resection site. There has been no evidence of recurrent abscess formation.

Discussion

Fonsecaea monophora is an infrequent cause of an uncommon condition, cerebral phaeohyphomycosis. The clinical spectrum of the cerebral manifestations caused by *F. monophora* and its response to treatment remain largely undefined. We report here the third case of *F. monophora* cerebral phaeohyphomycosis. Our patient was a distant cadaveric renal transplant recipient receiving only main-

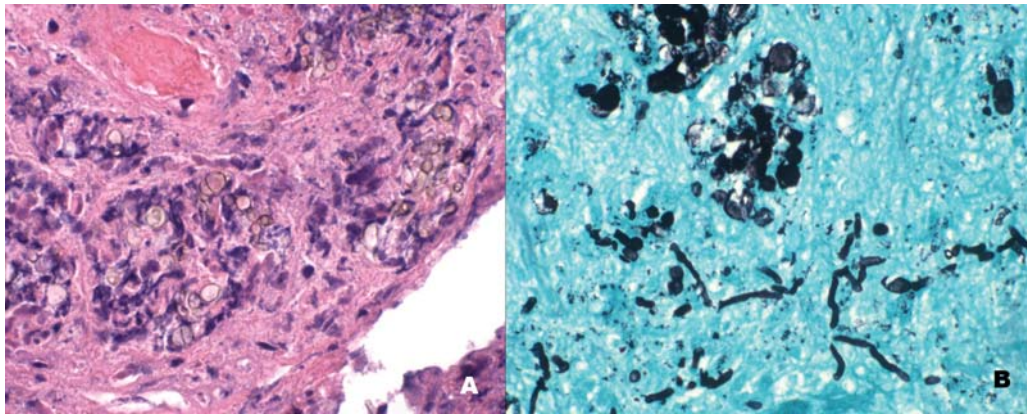

Fig. 2 Histopathology of resected brain abscess specimen showed granulomatous inflammation with pigmented hyphal and yeast-like structures on (A) H&E stain and (B) MSS stain.

tenance immunosuppressive therapy. She presented with severe headache but had minimal systemic symptoms or clinical findings. She was found to have a large left frontal lobe brain mass associated with extensive vasogenic edema and mass effect. After resection of her encapsulated mass, she received systemic parenteral liposomal amphotericin B and oral voriconazole until her pathology specimen was confirmed to show pigmented fungal forms suggestive of phaeohyphomycosis. Once the pigmented fungal forms were noted, the patient received voriconazole alone. Antifungal susceptibility testing of her *F. monophora* isolate demonstrated a voriconazole MIC of 0.125 μg/ml, and she completed 18 months of voriconazole monotherapy with full resolution of her symptoms and no evidence of recurrent abscess formation on serial brain imaging. Interestingly, her BG was markedly elevated at the time of diagnosis and gradually normalized with antifungal therapy. As with other previously reported *F. monophora* brain abscess cases, the origin of her infection remains cryptic. *F. monophora* is present in soil and decaying plant matter in tropical and subtropical climates and has commonly been reported as an agent of chromoblastomycosis in patients from these regions of the world [5,6]. However, the patient had not traveled to Jamaica in many years, and she had no cutaneous or pulmonary lesions on examination or imaging.

Two other *F. monophora* brain abscesses have been formally described in the literature to date [7,8]. There are also two other cerebral phaeohyphomycosis cases in which the etiologic organisms were initially identified as *Fonsecaea pedrosoi* [10] and *Cladophialophora bantiana* [11] which were subsequently reidentified as *F. monophora* based on retrospective sequencing of ribosomal internal transcribed spacer sequences [5]. Clinical features of all five known *F. monophora* brain abscess cases are summarized in Table 1.

Table 1 Clinical characteristics of five known patients with *Fonsecaea monophora* cerebral phaeohyphomycosis

Year reported	CBS[1] number	Age	Gender	Underlying condition[2]	CNS lesion[3]	Surgery	Maintenance antifungal regimen[4]	Outcome
1954(7)	100430	10	M	None	Multiple, exact location not reported	–	–	Death after 5 months
2003(8)	115830	28	M	None	Multiple, R temporo-occipital, L. occipital	Excision	ITRA	Death after 8 months, no fungal forms on autopsy
2005(9)	117238	53	M	Type II DM	Single, left frontal lobe	(1) Aspiration (2) Excision	(1) VORI + 5-FC (2) ITRA + 5-FC	Survival, discontinued antifungal therapy at 21 months
2007(6)	117236	62	F	OLT 4 months prior	Multiple, R anterior parietal, L parietal, L occipital	Excision R. parietal lesion	VORI	Survival, no recurrence at 18 months
2010	117542	48	F	CRT 8 years prior	Single, L inferior frontal lobe	Excision	VORI	Survival, discontinued antifungal therapy at 18 months

[1]CBS, Centraalbureau voor Schimmelcultures.
[2]DM, diabetes mellitus; OLT, orthotropic liver transplant; CRT, cadaveric renal transplant.
[3]R, right; L, left.
[4]ITRA, itraconazole; VORI, voriconazole; 5-FC, 5-flucytosine.

The first case developed in a 53-year-old tropical aquarium enthusiast from the United Kingdom who had no apparent underlying immune deficiencies or notable underlying conditions except for type II diabetes mellitus. This patient came to medical attention after a week of a right-sided headache, right upper and lower extremity weakness, and slurred speech [7]. Similar to our case, this patient had no fever, unremarkable examination findings except for his extremity weakness, and minimally elevated leukocyte counts and CRP despite the presence of a sizeable ring-enhancing lesion with extensive surrounding edema in his left frontal lobe. This patient's brain abscess cavity was initially aspirated rather than fully resected, and he received parenteral liposomal amphotericin B, then intravenous voriconazole and intravenous 5-fluorocystine (5-FC) when a dematiaceous fungus was recovered in cultures inoculated with tissue from his abscess cavity. This *F. monophora* isolate had low MICs to amphotericin B, itraconazole, voriconazole, and posaconazole. After three months of oral therapy with voriconazole and 5-FC, the patient had possible subarachnoid extension of his initial lesion on imaging and underwent full excision of his frontal lesion. Although fungal hyphae were visible in the pathologic sample, the authors reported no growth of fungi in cultures even after prolonged incubation. Despite ongoing therapy with voriconazole and 5-FC, the patient had progressive confusion, a progressively expanding lesion in his right suprasellar cistern, and a new lesion in his left thalamic region. His symptoms resolved and his imaging improved after voriconazole was switched to itraconazole with ongoing 5-FC. No antifungal drug levels were reported. This patient discontinued antifungal therapy 21 months after his initial presentation.

The second formally reported *F. monophora* cerebral phaeohyphomycosis case was described in a 62-year-old liver transplant recipient in Texas who presented with 5 months of progressive left upper extremity numbness and the more acute onset of pain in her left ankle 4 months after transplantation [8]. The patient had three distinct enhancing lesions in her right anterior parietal lobe, parasagittal left parietal lobe, and parasagittal left occipital lobe. She also had an area of enhancing marrow abnormality in her left medial malleolus. Examination of excisional biopsies of her medial malleolar lesion and right parietal brain lesion showed granulomatous inflammation and pigmented fungal organisms with numerous yeast-like cells and rare septate hyphae, scattered muriform cells. There was also a mixed inflammatory infiltrate with moderate eosinophils and scattered microabscesses. Tissue from biopsies of her bone and brain biopsy resulted in the isolation of *F. monophora*. She received oral voriconazole 200 mg twice daily for an unclear duration, and was reported to have no evidence of recurrence 1.5 years later.

The etiologic agents of two cases of cerebral phaeohyphomycosis were retrospectively reidentified as *F. monophora* based on DNA sequencing studies in 2004 [5]. The first case was reported in 1954 in a 10-year-old boy living in the Democratic Republic of the Congo (the Belgian Congo at the time of the case) who presented with 4 months of back pain refractory to quinine and penicillin, mild neck stiffness, and an occasional low-grade temperature [11]. Initial laboratory studies, spine X-ray, and an evaluation for infectious causes of his symptoms were unrevealing. He had progressive anemia and a mild eosinophilia three weeks later, and the filarial parasite *Mansonella perstans* was seen in his blood smear. The patient worsened clinically, and he received empiric penicillin, streptomycin, and antiparasitic therapy. Despite these measures, he had a progressive neurologic deterioration, with new seizures, a positive Kernig sign, nuchal rigidity, sluggish pupillary reflexes, diminished lower extremity reflexes, and a positive Babinsky sign bilaterally. His CSF was opalescent, with elevated protein levels and 245 cells per mm^3, mostly polymorphonuclear cells. All stains and cultures of his CSF were unrevealing. He had progressive neurologic deterioration and ultimately died five months after his initial presentation. He was noted to have on autopsy markedly dilated lateral ventricles with small black filaments floating in clear fluid and tiny black particles attached to the walls of his occipital horns. He had multiple small peripheral cerebral abscesses with a granulomatous response, some containing hyphal and spore-like forms. Cultures of his CSF grew a black fungus, thought at the time to represent *Cladosporium trichoides*.

The second retrospectively identified *F. monophora* brain abscess case occurred in a previously healthy 28-year-old man who presented with a severe headache, nausea, vomiting, right eye pain, and loss of the temporal field of vision in his right eye. A MRI of his brain showed a lesion in his right temporo-occipital area and a second smaller lesion in his left occipital lobe. His main right temporo-occipital lesion was surgically resected after approximately 3 weeks of systemic antifungal therapy with amphotericin B. The patient received 8 months of oral itraconazole 200 mg daily without evidence of disease recurrence [10]. Although this patient died from neurosurgical complications shortly afterwards, there was no evidence of fungal disease on autopsy.

Cerebral phaeohyphomycosis has historically been associated with mortality rates as high as 65% even after a combination of surgical resection and systemic antifungal therapy [1,2]. Due to the sporadic nature of these infections, optimal treatment strategies remain undefined. In a 2004 comprehensive review of all 101 cases of primary cerebral phaeohyphomycosis reported in the English-language literature, Revankar and colleagues found only

the combination of amphotericin B, 5-FC, and itraconazole was associated with improved clinical outcomes, with only one death in the 6 patients treated with this regimen [3]. Although the majority of successfully treated cerebral phaeohyphomycosis patients have received combination therapy, cases of successful treatment outcomes with voriconazole and posaconazole monotherapy have been reported since the advent of treatment with the extended-spectrum triazoles [12,13].

Of the four modern cases of *F. monophora* cerebral phaeohyphomycosis, three were treated with surgical resection of their primary lesion and azole monotherapy with apparent resolution of their infection. Two patients, both solid organ transplant recipients, were successfully treated with voriconazole [8], while a third received itraconazole with no evidence of residual fungal infection on autopsy after his death from neurosurgical complications. The fourth patient was initially treated with aspiration of his brain abscess rather than a full surgical resection but then had evidence of progressive infection on voriconazole and 5-FC despite the low voriconazole MIC of his isolate. He ultimately improved after surgical resection of his lesion followed by itraconazole and 5-FC therapy.

A combination of surgical excision and azole monotherapy appears to be a viable treatment strategy in patients with *F. monophora* cerebral phaeohyphomycosis if the clinical isolate suggests *in vitro* sensitivity. Given the rarity of *F. monophora* infections to date, no susceptibility standards for voriconazole or other antifungal drugs exist. In our experience, confirming antifungal trough drug levels higher than the MIC of the infecting isolate has been a useful adjunct in the clinical management of these cases, especially when drug interactions are likely to occur. BG appears to have value in diagnosis and therapeutic response monitoring in these infections.

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