

Case report

Cerebral phaeohyphomycosis caused by *Fonsecaea monophora*

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We report a case of cerebral phaeohyphomycosis in a 53-year-old immunocompetent diabetic male, caused by *Fonsecaea monophora*. Computerized tomography of the brain revealed an abscess, which yielded *F. monophora* in pure culture. The patient's condition deteriorated on treatment with voriconazole and 5-fluorocytosine, and improved subsequently with high-dose itraconazole. The genus *Fonsecaea* has recently been revised and the new species *F. monophora* generated from molecular analysis of isolates, most of which were originally identified as *Fonsecaea pedrosoi*. This is the fourth case of cerebral infection known to have been caused by *F. monophora*, although only the first reported as such. These cases suggest that the clinical potential of *F. monophora* differs from that of *F. pedrosoi*, one of the main agents of chromoblastomycosis, with *F. monophora* being predominantly neurotropic in the human host.

Keywords *Fonsecaea*, phaeohyphomycosis, cerebral, infection, brain

Introduction

Phaeohyphomycosis is a collective term used for fungal infections caused by moulds and yeasts that have brown-pigmented cell walls due to the presence of melanin (dematiaceous fungi). The numerous species that have been reported to cause phaeohyphomycosis are mainly members of the fungal orders Pleosporales (*Alternaria*, *Bipolaris*, *Curvularia*, *Exserohilum*) and Chaetothyriales (particularly *Cladophialophora*, *Exophiala* and *Ramichloridium*) [1].

Fungal brain infections are classically described in immunocompromised patients, caused by fungi with hyaline cells such as *Cryptococcus neoformans*, *Aspergillus* spp., *Pseudallescheria* and the Zygomycetes. However, in a comprehensive review of 101 cases of cerebral phaeohyphomycosis reported between 1996

and 2002, over half the cases reported were in immunocompetent patients [2], and the propensity for this condition to arise in otherwise healthy people has been well described in other reviews [3,4]. Cerebral phaeohyphomycosis, therefore, is largely a disease of the immunocompetent host.

The most frequent causes of cerebral phaeohyphomycosis are *Cladophialophora* (formerly *Xylohypha*) *bantiana* and *Ramichloridium mackenziei*, although several other dematiaceous fungi have been implicated [2]. In this report a case of cerebral phaeohyphomycosis caused by the recently described dematiaceous fungus *Fonsecaea monophora* is described. This species was recently segregated from *Fonsecaea pedrosoi* [5], one of the main etiologic agents of human chromoblastomycosis. *F. monophora* was shown to have a more variable clinical spectrum than *F. pedrosoi* [5] and included a strain that had caused a cerebral infection in a human patient, although reported as *F. pedrosoi* [6]. The clinical significance of *F. monophora* as a potential agent of cerebritis is underlined by this case report.

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Case report

A 53-year-old Caucasian male was referred for neurosurgical assessment after the detection of a left frontal lesion on a computerized tomography (CT) scan. He gave a one-week history of right-sided weakness, slurred speech and a constant dull right-sided headache. During this period his general practitioner had made a diagnosis of right-sided otitis media, which was treated with amoxicillin. Six months previously he had suffered from an influenza-like illness, and had again been diagnosed with right-sided otitis media, which resolved on treatment with amoxicillin. This illness had also been accompanied by weakness of his right arm and leg, which had resolved spontaneously. His remaining medical history consisted of hypertension, type II diabetes mellitus (DM) and a previous peptic ulcer. Medications on admission were lansoprazole and gliclazide. His DM had been diagnosed at his referring hospital on the basis of a single plasma glucose level of 15 mM, following a two-week history of thirst and polyuria.

On examination he had grade 4/5 power (MRC grading) in his right arm and legs. He was apyrexial, and physical examination was otherwise entirely normal. The results of admission blood tests were: haemoglobin 13.7 g/dl, leucocyte count $11.8 \times 10^9/l$ (neutrophils $7.91 \times 10^9/l$, lymphocytes $2.13 \times 10^9/l$), C-reactive protein 8 mg/l, plasma glucose 5.8 mM. A CT scan of his brain demonstrated a 3.6 cm \times 2.3 cm ring-enhancing lesion in the left frontal lobe, with surrounding oedema, which is shown in Fig. 1A.

He was admitted immediately for drainage of the frontal lesion, which was undertaken through a left frontal burr hole. The capsule was difficult to puncture, however a viscous, greenish-yellow, fluid with no foul smell was aspirated and submitted for microbiological examination. Gram-staining of the aspirated fluid revealed septate fungal hyphae, with no bacteria or white blood cells. It was not possible to assess the hyphae for the presence of pigment due to the effect of the Gram-staining reaction. The patient was commenced on intravenous liposomal amphotericin B (Ambisome®) 6mg/kg/day. The abscess fluid was cultured on Sabouraud dextrose agar supplemented with chloramphenicol (500 mg/l) and incubated at 27°C and 37°C and on a range of selective and non-selective bacteriological media in both aerobic and anaerobic conditions. After seven days a dematiaceous fungus was isolated in pure culture on Sabouraud's agar; bacterial cultures remained sterile and were discarded. At this time CT of the brain showed a modest reduction in the size of the lesion. A diagnosis of cerebral phaeohypho-

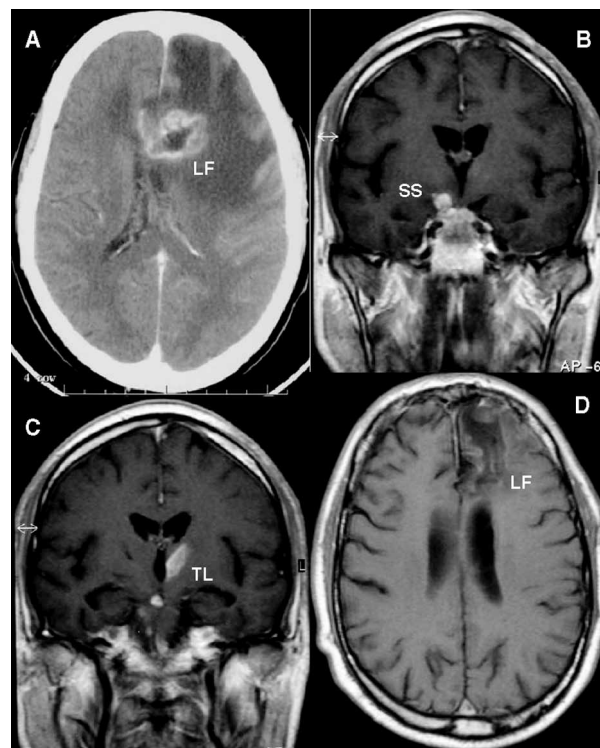


Fig. 1 Disease progress monitored by computerized tomography (CT) and magnetic resonance imaging (MRI). A, left frontal lesion (LF) at initial presentation (CT); B, supra-sellar extension (SS) after four months antifungal therapy (MRI); C, left thalamic lesion (TL) after five months' antifungal therapy (MRI); D, residual appearance of left frontal (LF) lesion 12 months after excision of the fungal lesion (MRI).

mycosis was made on the basis of the isolation of a dematiaceous fungus from a brain lesion, and antifungal therapy was changed to intravenous voriconazole 6 mg/kg bd (reduced to 4 mg/kg after 24 h) and intravenous 5-fluorocytosine (5-FC) 2 g daily. The route of administration of both drugs was subsequently changed to oral, and they were continued for five months. Target serum concentrations of 5-FC were 20–40 mg/ml (pre-dose) and 70–90 mg/ml (post-dose). Average concentrations achieved were 33.9 mg/ml (pre-dose) and 62.35 mg/ml (post-dose).

The fungus was provisionally identified as *Cladophialophora* spp., and referred to the Centraalbureau voor Schimmelcultures (CBS, Utrecht, The Netherlands). The strain was deposited in the CBS culture collection with the accession number CBS 117238. The identification of the present strain was done by sequencing of the rDNA Internal Transcribed Spacer (ITS) region and comparison with a large black yeast data base maintained at CBS for research purposes. It was identified formally as *F. monopora*, on the basis of close sequence identity with the ex-type strain, CBS

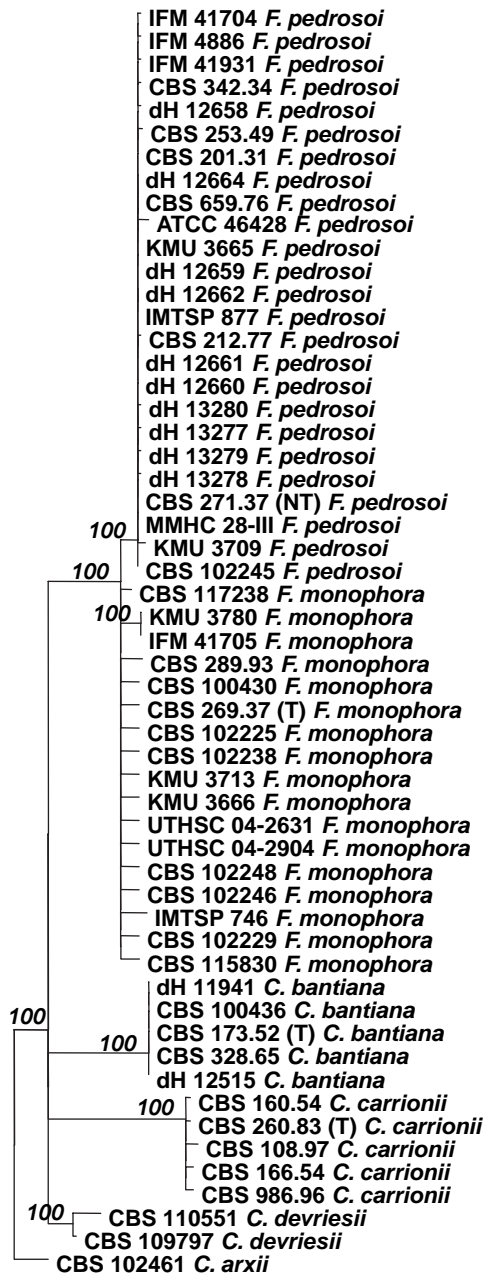


Fig. 2 Phylogenetic tree of *Fonsecaea* and relatives based on confidently aligned ITS rDNA sequences using Neighbor joining algorithm with Kimura (2) correction. Bootstrap values >90 from 100 resampled datasets are shown; branches with lower values are shown as unresolved.

269.37. The comparison with described *Fonsecaea* species and some morphologically similar systemic fungi is shown as a phylogenetic tree in Fig. 2, with the list of strains analysed given in Table 1.

The two *Fonsecaea* species are separated by consistent, phylogenetically informative polymorphisms in 10 bases, listed in Table 2. Two strains, including CBS

117238, showed two of these mutations that were characteristic for *F. pedrosoi*, but nine that were characteristic for *F. monophora*. Identification of our strain as *F. monophora* is thus justified. This is in accordance with morphology, shown in Fig. 3, the frequent occurrence of 3-celled conidial chains being a hallmark of the species.

Antifungal susceptibility testing was carried out at the University of Texas Health Science Centre Fungus Testing Laboratory, San Antonio, Texas, USA. Minimum inhibitory concentrations at 96 h were: amphotericin B 0.5 mg/l, itraconazole 0.03 mg/l, voriconazole 0.06 mg/l and posaconazole <0.015 mg/l.

After a month of antifungal therapy the size of the lesion remained static. It was discovered at this time that the patient was a keeper of tropical fish. One year previously he had acquired an aquarium containing tropical fish and aquatic plants. The fish are believed to have originated from the South American Amazon basin, and the plants from Malaysia. Unfortunately both fish and plants had been sold to another collector, and were not therefore available for mycological examination. The patient was investigated for the presence of a possible primary fungal lesion or immune defect. There were no apparent skin lesions; ear, nose and throat examination were unremarkable; chest radiography and echocardiography were normal; anti-HIV antibodies were not detected; complement and immunoglobulin levels were within normal limits, although serum IgA was marginally below the lower limit of normal, at 0.54 g/l (local reference range 0.8–4 g/l).

After three months of antifungal therapy his progress was monitored by magnetic resonance imaging (MRI). The left frontal lesion had not reduced in size, and there was meningeal thickening in the region of the pons, which was consistent with sub-arachnoid extension of the initial lesion. The frontal lesion was excised completely via a left frontal craniotomy, with tissue samples sent for microbiological examination. On microscopy, fungal hyphae were seen in several of these samples, although no fungi were isolated, despite incubation on mycological media for three weeks. Bacterial culture also remained negative. The histopathological appearance of the excised brain tissue at this time was that of an abscess with a necrotic centre and a dense fibrous tissue capsule, containing brown, septate, branching hyphae with occasional bulbous elements (see Fig. 4). There was cellular infiltration by neutrophils, foamy macrophages, haemosiderin-laden macrophages, lymphocytes and multinucleated giant cells. The patient was maintained on 5FC and voriconazole. A month later MRI revealed extension of

Table 1 List of strains studied for comparison. ATCC, American Type Culture Collection, Manassas, USA; CBS, Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands; CDC, Centers for Disease Control and Prevention, Atlanta, USA; dH, G.S. de Hoog working collection at CBS; FMC, collection D. Borelli, Caracas, Venezuela; IFM, Research Institute for Pathogenic Fungi, Chiba, Japan; IMTSP, Instituto de Medicina Tropical, São Paulo, Brazil; KUM, Department of Dermatology, Kanazawa, Japan; MMHC, Medical Mycology Hospital das Clínicas, Curitiba, Brazil; MUCL, Mycotheque de l'Université de Louvain, Louvain-la-Neuve, Belgium; UAMH, Microfungus Herbarium and Collection, Edmonton, Canada; UNEFM, Universidad Nacional Experimental Francisco de Miranda, Coro, Venezuela; UTHSC, Fungus Testing Laboratory, Department of Pathology, University of Texas Health Science Center at San Antonio, USA.

Strain number	Genbank	Other ref.	Substrate	Origin
<i>Fonsecaea pedrosoi</i> :				
Bonifaz 150-89	AY366906	dH 12659	Chromoblastomycosis	Mexico
Bonifaz 608-99	AY366907	dH 12662	Chromoblastomycosis	Mexico
Bonifaz 938-98	AY366910	dH 12664	Chromoblastomycosis	Mexico
Bonifaz 521-00	AY366909	dH 12661	Chromoblastomycosis	Mexico
Bonifaz 120-01	AY366908	dH 12658	Chromoblastomycosis	Mexico
Bonifaz 592-01	AY366911	dH 12660	Chromoblastomycosis	Mexico
CBS 212.77	AY366912		Chromoblastomycosis	Netherlands
CBS 201.31	AY366913		Ear of gazelle	Lybia
CBS 271.37	AY366914	ATCC 18658	Chromoblastomycosis	S America
CBS 342.34	AY366915		Chromoblastomycosis	Puerto Rico
CBS 273.66	AY366916		Soil/mouse passage	Venezuela
CBS 102245	AY366918	MMHC 28-III	Chromoblastomycosis	Brazil
CBS 272.37	AY366917	MMHC 63I	Chromoblastomycosis	Brazil
CBS 102247	AY366919	MMHC 77-II	Chromoblastomycosis	Brazil
CBS 659.76	AY366920	ATCC 28303	Chromoblastomycosis	S America
CBS 285.47			Chromoblastomycosis	Puerto Rico
CBS 274.66			Soil/mouse passage	Venezuela
CBS 102244		MMHC 37-II	Chromoblastomycosis	Brazil
CBS 670.66			Soil/mouse passage	Venezuela
CBS 671.66			Soil/mouse passage	Venezuela
CBS 253.49	AY366921		Chromoblastomycosis	Uruguay
		ATCC 46428	Chromoblastomycosis	Brazil
IMTSP 877	AY366922		Chromoblastomycosis	Brazil
CBS 277.29			Chromoblastomycosis	Brazil
CBS 269.64			Chromoblastomycosis	Cameroon
UNEFM-R4		dH 13280	Plant debris	Venezuela
UNEFM-9807		dH 13277	Chromoblastomycosis	Venezuela
UNEFM-95009B		dH 13278	Chromoblastomycosis	Venezuela
UNEFM-9301		dH 13279	Chromoblastomycosis	Venezuela
		IFM 41931, IFM 41704, IFM 4886, KUM 3665, KUM 3709	All unknown	
<i>Fonsecaea monophora</i> :				
IMTSP 746	AY366923		Chromoblastomycosis	Brazil
CBS 100430	AY366924	ATCC 32280	Brain, human	Africa
HC2			Lesion in immunocompromised	Brazil
CBS 269.37			Chromoblastomycosis	S America
CBS 397.48		ATCC 9475	Chromoblastomycosis	Brazil
CBS 289.93	AY366925		Seabear	Netherlands
CBS 102248	AY366926	MMHC 82	Chromoblastomycosis	Brazil
CBS 102242		MMHC 26-III	Chromoblastomycosis	Brazil
CBS 102243		MMHC 31-I	Chromoblastomycosis	Brazil
CBS 102238	AY366927	MMHC 1PLE	Soil	Brazil
CBS 102229		MMHC	Litter	Brazil
CBS 102246	AY366928	8DPIRA = dH 11590		
CBS 102225		MMHC 65I	Chromoblastomycosis	Brazil
CBS 102223		MMHC 5P4 = dH 11584	Rotten wood	Brazil
CBS 117238		MMHC CL2 = dH 11583	Rotten root	Brazil
		dH 13130 = UTHSC	Brain, human	UK
		R-3486		
		IFM 41705	Bark	China

Table 1 (Continued)

Strain number	Genbank	Other ref.	Substrate	Origin
		KUM 3713, KUM 3780, KUM 3666	All unknown	
CBS 115830		UTHSC 04-2631 UTHSC 04-2904 dH 12978	Leg, human Brain, human Brain, human	USA USA Brazil
<i>Cladophialophora bantiana:</i>				
RKI 116/2000		dH 11941	Brain, human	Germany
CBS 100436		ATCC 58039	Brain, cat	California
CBS 173.52			Brain, human	USA
CBS 328.65		CDC	Liver, dog	Curacao
UTMB 5459		B-3394 = NCMH 1168 dH 12515	Chromoblastomycosis	Mexico
<i>Cladophialophora carrionii:</i>				
CBS 260.83		CDC B-1352 = FMC 282	Skin lesion	Uganda
CBS 108.97		UNEFM 9501	Chromoblastomycosis	Venezuela
CBS 160.54		ATCC 16264 = CDC A-835 = MUCL 40053	Chromoblastomycosis	Australia
CBS 166.54		MUCL 10088	Human skin	Venezuela
CBS 986.96		UAMH 5717	Clinical specimen	Canada
<i>Cladophialophora devriesii:</i>				
CBS 110551			Oil-polluted soil	Netherlands
CBS 109797		dH 11474	Filter	Germany
<i>Cladophialophora arxii:</i>				
CBS 102461	CDC B-5881		Brain, human	

the new lesion within the right supra-sellar cistern and the adjacent anterior interhemispheric fissure (Fig. 1B); after another month MRI revealed further extension of the lesion around the supra-sellar area, and another lesion in the left thalamus (Fig. 1C). At this time the patient had developed confusion, loss of short-term memory and diplopia. His abbreviated mental test score (AMTS) was 2/10. Neurological examination, including cranial nerves, peripheral nerves and visual fields, revealed no other deterioration. Microbiological examination of cerebrospinal fluid (CSF) revealed a raised leucocyte count (white cell count $95 \times 10^6/l$, predominantly lymphocytes). At lumbar puncture,

CSF opening pressure was 16 cm H₂O. CSF protein was 1.46 g/l (local reference range 0.2–0.4 g/l) and CSF glucose was 1.9 mmol/l (plasma glucose was not measured for comparison at this time). Bacterial and fungal cultures of CSF were negative despite prolonged incubation. In view of the extension around the supra-sellar area, pituitary function was assessed by full hormone profile (TFT/LH/FSH/Testosterone/SHBG/IGF-1/HbA1c/Prolactin), glucagon stimulation tests and formal visual field testing, the results of which were normal.

In view of his clinical deterioration and possible meningeal involvement voriconazole was stopped and

Table 2 Phylogenetically informative polymorphic sites in *Fonsecaea*. Lengths of ITS spacers and 5.8S gene are mentioned in brackets. Prevalent bases in *Fonsecaea pedrosoi* vs. *Fonsecaea monophora* are listed, with less common mutations in brackets.

ITS 1 (1-222) Position:	25	52	58	73	77	91	111	112	122	135	151
<i>Fonsecaea monophora</i>	T	T	T(A)	C	A	G(T)	T	C(T)	C	G	T(C)
CBS 117238	T	T	A	C	A	T	T	C	C	G	T
<i>Fonsecaea pedrosoi</i>	C	C	A	C(T)	A(T)	T	C	T	T	A(G)	T
5.8S (223–383)											
ITS 2 (384–607) Position:	429	430	438	479	502	504	528	553	567	576	
<i>Fonsecaea monophora</i>	T	A	A(G)	A(G)	A	C	C	-	-	C	
CBS 117238	C	A	A	A	A	C	T	-	-	C	
<i>Fonsecaea pedrosoi</i>	C	G	A	A	T	T	T	-(C)	-(T)	T	

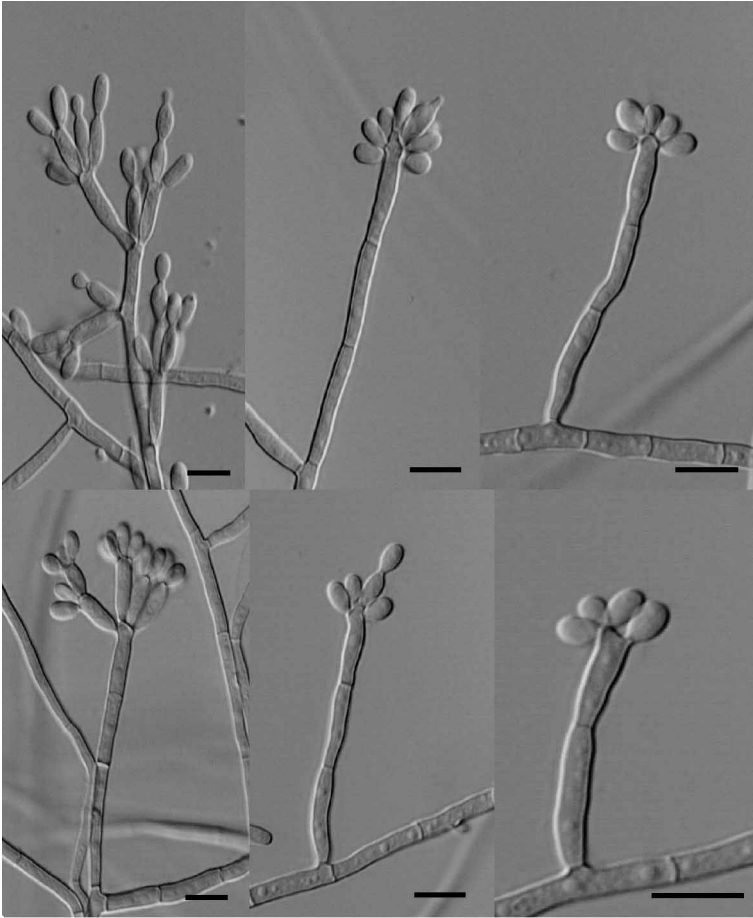


Fig. 3 Microscopic appearance of *Fonsecaea monophora*, CBS 117238, showing young and mature conidial heads with chains of maximally 3 conidia. Marker bars represent 5 μ m in all pictures.

replaced with intravenous itraconazole 400 mg tds for 24 h, and subsequently 200 mg tds. He remained on oral 5-FC at a dose of 2.5 g bd.



Fig. 4 Brain tissue from left frontal lesion excised after three months of antifungal therapy, stained with Grocott's silver stain. Only the fungus is visible in this section as the background cellular material does not stain with Grocott's stain.

After two weeks of intravenous itraconazole his confusion improved. Treatment was changed to oral itraconazole 300 mg bd and 5-FC as above. During the next two months he had serial MRI scans, which showed improvement in his left thalamic lesion. The appearance of the brain stem lesions remained unchanged. Eighteen months after the diagnosis of cerebral phaeohyphomycosis, his clinical condition had continued to improve, with normal neurological examination findings and a slightly improved AMTS of 4/10. MRI 12 months after excision of the frontal lobe lesion showed good resolution of the lesion (Fig. 1D). Twenty-one months after his initial diagnosis his clinical and radiological condition remained stable and his antifungal treatment was stopped.

Discussion

Although there is some controversy in the literature about the nomenclature of diseases caused by dematiaceous fungi, this can reasonably be described as a case of cerebral phaeohyphomycosis [1]. The reader is referred to several recent reviews, in which the predis-

posing factors, clinical presentations, treatment and outcomes of cases of cerebral phaeohyphomycosis were discussed in detail [2–4]. Twenty-four fungal species have been implicated in cerebral phaeohyphomycosis [2]. Most of these species cause secondary cerebral infection, arising in other sites (most often the sinuses) before spreading to the brain. However, four species can be considered to be neurotropic, namely *Cladophialophora bantiana*, *Exophiala dermatitidis*, *Ramichloridium mackenziei* (Chaetothyriales), and *Ochroconis gallopava*, whose phylogenetic relationship is thus far unknown [3,4]. These species have caused human brain infections in multiple patients and exhibit primary neurotropism, i.e. causing brain infection not associated with secondary spread from other sites [4]. The most common species, *C. bantiana*, has a worldwide distribution [2]. Cerebral infections by *E. dermatitidis* are observed only in East Asia [7], while *R. mackenziei* is strictly limited to the Middle East [8]. Less than half of the cases caused by *C. bantiana* were associated with an underlying disease or risk factor, and in only a single case was the predisposing factor diabetes mellitus. Mortality was similar in immunodeficient and immunocompetent patients (71% and 74% respectively). Also the other two species have a significant share of hosts without known underlying disease [2].

In older literature, several cerebral cases were attributed to *F. pedrosoi*. Fukushima [9] mentioned eight cases of brain infection by this species. However, some of the strains reported in Fukushima's paper were verified to be *E. dermatitidis* on the basis of ITS sequence data [10]. The re-classified strains probably exhibited a preponderantly catenulate morphology, as described by de Hoog *et al.* [11], at the time of isolation. Isolates from cerebral cases in the Middle East published under the name *F. pedrosoi* [12] were later accommodated in the species *R. mackenziei* [13].

One of the *F. pedrosoi* cerebritis cases, reported from South America [6], was confirmed subsequently to have been caused by *F. monophora* [5]. Furthermore, an earlier case from Africa, published under the name *C. bantiana* [14], was re-identified in the course of this study as *F. monophora*. Recently *F. monophora* was isolated from the brain of a patient who also had cutaneous lesions (D. A. Sutton, personal communication). Consequently, out of the 12 strains of *F. monophora* isolated from clinical specimens up to now and shown in Table 1, four have involved primary brain infection. The majority of the remaining clinical strains originate from cases of chromoblastomycosis [5]. While separating the two closely related *Fonsecaea* species, de Hoog *et al.* (2004) [5] noticed that the

clinical spectra were different: *F. pedrosoi* seems to be a pathogen strictly associated with chromoblastomycosis, while *F. monophora* is an opportunist with a more variable clinical spectrum. *F. monophora* may be regarded as the fourth species of Chaetothyriales that exhibits marked neurotropism.

The origin of the *F. monophora* infection in this case is obscure. The natural habitat of this fungus may be putrid plant material, as several strains from dead plants and soil were identified as this species [5]. Its geographic distribution is mainly in tropical South America and Africa. There is a possibility that the fungus was related to the patient's keen interest in tropical aquaria, specifically his South American fish and South-east Asian aquatic plants. However, this cannot be confirmed. Furthermore the portal of entry of the fungus is unclear. Direct spread seems unlikely. Although he had suffered from otitis media this was on the opposite side to his subsequent brain lesion. There was no evidence of a cutaneous or pulmonary lesion which could have been the source of haematogenous spread. The most likely portal would seem to be inhalation, followed by direct or haematogenous spread, with subsequent localization in the cerebral cortex and local spread.

The only known underlying disease in this patient was diabetes mellitus. This had been diagnosed shortly before his initial presentation and was well controlled. Random blood glucose levels remained within normal limits during and after his hospital admission (4.4 mM and 3.9 mM at 3 and 6 months post-presentation respectively). There was no history of ketoacidosis, which is known to predispose to fungal infection, although specifically zygomycosis rather than phaeohyphomycosis [15]. The authors are aware of only a single previous case of cerebral phaeohyphomycosis where the predisposing factor was diabetes mellitus [16]. In that case the causal agent was *Cladophialophora bantiana*: the patient relapsed during treatment with amphotericin B after initial excision of the lesion, and made a full recovery after re-excision and treatment with itraconazole and 5-FC.

Because of the rarity of cerebral phaeohyphomycosis there is no consensus concerning the most appropriate antifungal treatment. In this case the initial antifungal regimen (Ambisome®) was chosen as it is a broad-spectrum agent with the best penetration into the brain of all available amphotericin B formulations [17]. Voriconazole was chosen subsequently because of its known activity against dematiaceous fungi [18] and its penetration into the CNS and brain [19]. Similarly 5-FC is active and has good bioavailability in the CSF [20]. Itraconazole was chosen because of its known

activity against dematiaceous fungi and reports of its clinical utility in phaeohyphomycosis, including cerebral phaeohyphomycosis [6,16,21]. Although bioavailability of itraconazole in CSF is poor, penetration into the brain is good [22]. The case of *F. monophora* cerebral phaeohyphomycosis that was reported as *F. pedrosoi* was treated with a short course of amphotericin B deoxycholate, followed by oral itraconazole 200 mg/day for eight months. After this time the patient died from complications of neurosurgery, and was found to have no evidence of residual fungal infection at *post mortem* [6]. Although there is no standard antifungal treatment for the treatment of cerebral phaeohyphomycosis it is generally agreed that a combination of medical and surgical treatment is required [3,23]. Based on the available evidence it would seem that a combination of surgical excision and itraconazole is an appropriate treatment for cerebral phaeohyphomycosis caused by *F. monophora*.

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