Medical Mycology, 2016, 54, 111–119
doi: 10.1093/mmy/myv091
Advance Access Publication Date: 18 October 2015
Original Article

Original Article

Brain abscess due to *Cladophialophora bantiana*: a review of 124 cases

Arunaloke Chakrabarti[1], Harsimran Kaur[2], Shivaprakash M Rudramurthy[3,*], Suma B Appannanavar[4], Atul Patel[5], Kanchan K Mukherjee[6], Anup Ghosh[7] and Ujjwayini Ray[8]

[1]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [3]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [4]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [5]Vedanta Institute of Medical Sciences, Ahmedabad, India, [6]Department of Neurosurgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [7]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India and [8]Department of Microbiology, Apollo Gleneagles Hospitals, Kolkata, India

*To whom correspondence should be addressed. Dr. Shivaprakash M Rudramurthy, Additional Professor, Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India – 160012. Tel: +91-172-2755162/2755172; Fax: +91-172-2744401/2745078; E-mail: mrshivprakash@yahoo.com

Received 5 June 2015; Revised 28 July 2015; Accepted 8 September 2015

Abstract

Brain abscess caused by *Cladophialophora bantiana* is a rare disease associated with high mortality due to delay in diagnosis and absence of standardized therapy. We reviewed 124 culture proven *C. bantiana* brain abscess cases; 103 cases published in English literature during 1952 through 2014 and 21 unpublished cases from our reference center. The majority (57.3%) of the patients was from Asian countries especially from India (62/124, 50%). The diagnosis of the cases was delayed with mean duration 115 days after developing symptoms. The disease was nearly equally distributed in immunocompetent and immunosuppressed hosts but associated with significantly higher mortality (77.1%) in later group. Complete excision of brain lesion in immunocompetent host led to significantly better survival (43.7%). Though all commercially available antifungal drugs have been used in these patients, amphotericin B deoxycholate or lipid preparations were most commonly (62.83%) prescribed agent. None of the drugs used was found to be independently associated with improved outcome. *In vitro* antifungal susceptibility testing of 13 isolates of our center, demonstrated good activity to voriconazole, posaconazole, and itraconazole, but these triazoles were prescribed in only 29.2% patients. Increased awareness with early suspicion of the disease, and aggressive medical and surgical approach in treating these patients may improve the outcome.

Key words: brain abscess, *Cladophialophora bantiana*, phaeohyphomycosis, antifungal.

Introduction

Cladophialophora bantiana is the most common melanized mycelial fungus causing brain abscess (nearly 50% of brain abscess due to melanized fungi).[1] It poses as a serious threat due to the associated high mortality. The disease is reported both in immunocompromised and immunocompetent hosts with male predominance for unknown reason. Though the disease is prevalent worldwide, considerable number of cases have been reported from Asian countries especially from India.[2]

C. bantiana is a ubiquitous soil saprophyte inhabiting living and dead plant material. The exposure to soil and plant matter possibly leads to paranasal sinus or pulmonary infection, whereas traumatic inoculation causes subcutaneous infection.[2] The fungus may involve the brain by direct extension from sinuses or via blood or lymphatics from primary site of infection such as lungs or subcutaneous tissue. In the brain, the infection presents as space occupying lesion mimicking tumour, tuberculosis or other microbial infection.[3] Due to relative rarity of the disease and lack of specific symptoms and signs, the disease is difficult to diagnose *ante mortem*, and many cases are diagnosed accidentally during surgery or autopsy. The early diagnosis and appropriate therapy remain a challenge in such patients.

There is hardly any case series describing the clinical course, therapy, and outcome of the disease. As *C. bantiana* brain abscess is comparatively more prevalent in India, we reviewed the cases recorded at our referral center and those reported in the literature to evaluate the descriptive epidemiology and clinical characteristics, therapeutic regimen practised, and the outcome of the disease.

Methods

Cases at our mycology referral center, Chandigarh

The microbiology records (from 2004 through 2014) were reviewed to identify the brain abscess cases due to *C. bantiana*. In addition, the cases referred to this reference centre from laboratories across the country were included. The medical records of all these cases were analysed to evaluate demography, clinical characteristics, management, and outcome. Identity of all the isolates were confirmed both by phenotypic and molecular characters. The molecular identification was done by sequencing the ITS portion of ribosomal DNA. The antifungal susceptibility testing of the isolates was performed for available 13 clinical isolates using microbroth dilution technique in accordance with CLSI guidelines (M38/A2 protocol) for amphotericin B, fluconazole, itraconazole, voriconazole, posaconazole, and three echinocandins (caspofungin, anidulafungin, micafungin).[4]

Literature search

Medline (National Library of Medicine, Bethesda, MD, USA) was searched for the period 1952 to 2014 with terms 'brain abscess', 'melanized fungi', 'phaeohyphomycosis', 'cerebral', 'meningitis', '*Cladophialophora bantiana*', '*Xylohypha bantiana*', and '*Cladosporium trichoides*'. Only cases from English literature were reviewed. A case of brain abscess, localized or as part of disseminated disease, due to culture proven *C. bantiana* were included in the review.

Statistical analysis

The data were analyzed using SPSS 17.0 (SPSS Inc, Chicago, IL). The data are presented as frequencies and percentages or means and standard deviation (SD). The categorical variables were compared by Pearson's χ^2 test and Fisher's exact test, while Student's *t*-test was used to compare continuous data. The logistic regression was used to formulate a predictive model for mortality. A P value $<.05$ was considered as significant.

Results

Of 409 brain abscess samples processed at our center over the period of 2004 through 2014, 33 cases (8.1%) were due to fungi and *C. bantiana* was isolated from 5 (15.2%) cases. Additionally, 16 *C. bantiana* brain abscess cases with their isolates were referred to us from various parts of our country for confirmation of diagnosis or identification of isolates.

From literature search additional 103 cases of brain abscess due to *C. bantiana* were identified. The worldwide distribution of *C. bantiana* brain abscess cases is depicted in Figure 1. The available data on clinical characteristics, management and outcome of 124 cases were analyzed. The majority (n = 71, 57.3%) of *C. bantiana* brain abscess were from Asian countries, and 53 (42.7%) were from other continents; India was the major contributor (n = 62, 87.3%) of cases from Asian countries (Fig. 1). The number of patients diagnosed in India increased considerably during last four years (2011–2014). Among patients from other continents (n = 53), 32 were from North America, 11 from Europe, 4 from Africa, 5 from South America, and 1 from Australia. Males (88, 73.3%) with mean age of 40 ± 17.8 years were common sufferers. The data on rural or urban origin of the patients were available in 49 patients; 40 (81.6%) of them were from rural origin.

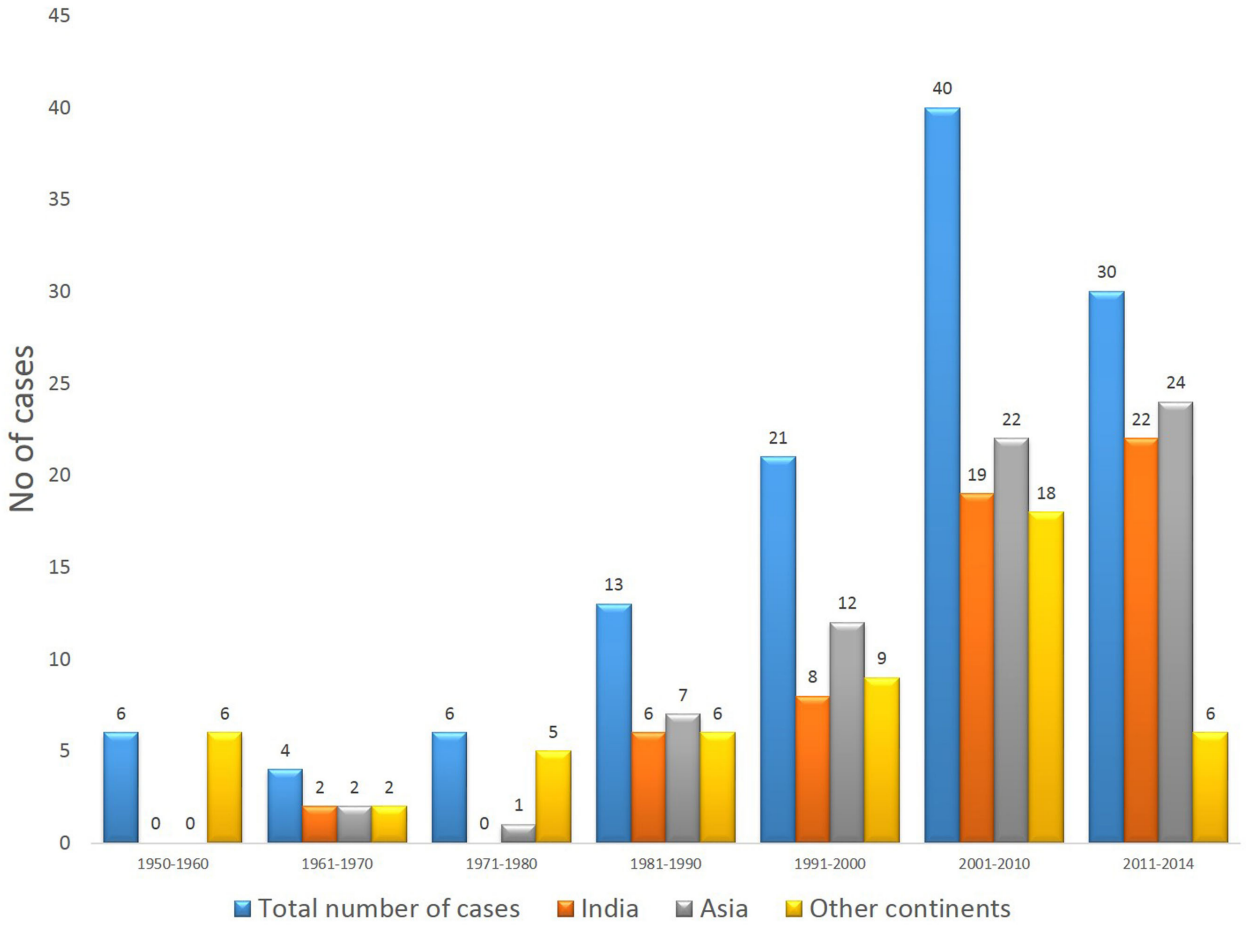

Figure 1. Worldwide distribution of *Cladophialophora bantiana* brain abscess cases from 1950 to 2014. This Figure is reproduced in color in the online version of *Medical Mycology*.

Clinical characteristics

The salient clinical features of *C. bantiana* brain abscess cases are given in Table 1 and Supplementary Table 1. The majority (71/120, 59.2%) of the patients were immunocompetent. Among immunosuppressed patients (n = 49, 40.8%), long-term steroid use was noted in 24 patients, solid organ transplantation in 19 patients, immunosuppressive therapy in 6 patients, malignancy in 5 patients, and one patient had AIDS (Table 1 and Supplementary Table 1). Ten patients had uncontrolled diabetes, and one had tuberculosis as comorbidity. The patients presented with headache (56.1%), hemiparesis (54.2%), seizures (31.8%), altered sensorium (30.8%), fever (22.4%), vomiting (18.7%), aphasia/dysarthria (14.9%), and visual disturbance (11.2%). The majority (92.9%) of the patients had localized brain abscess, and 8 (7.1%) immunosuppressed patients developed brain abscess as a part of disseminated disease. Single lesion was noted in 74 (67.3%) patients, while multiple lesions were noted in 36 (32.7%) patients (Table 1 and Supplementary Table 1). In the order of frequency, the lesions were in frontal (53.1%), parietal (42.3%), or occipital (10%) region. The ring enhancing lesion on radiology (CT or MRI) was noted in 87 (84.5%) patients. Thirteen (11.9%) patients had meningitis in addition to brain abscess. Cerebrospinal fluid (CSF) examination revealed sugar (mean 53 ± 32.74 mg/dl), protein (mean 236.21 ± 513.94 mg/100 ml) and cells (mean 542 ± 969.012 cubic mm) with neutrophil predominance.

Therapy

The antifungal treatment history could be evaluated in 113 patients (Table 1 and Supplementary Table 1). A complete excision of lesion was performed in 52 (46.4%) patients, partial excision in 41 (36.7%) patients. The antifungal therapy was instituted in 90 (78.2%) patients. The therapy included amphotericin B deoxycholate (48.7%), 5-fluorocytosine (18.5%), voriconazole (17.7%), combination of amphotericin B and 5-fluorocytosine (15.3%), lipid preparations of amphotericin B (14.2%), fluconazole (14.2%), posaconazole (3.5%), itraconazole (7.9%), echinocandins (3.5%), and ketoconazole (1.8%).

Table 1. Comparison of clinical characteristics of patients with brain abscess due to *Cladophialophora bantiana* in two regions (Asia and other continents).

Clinical characteristics	Total [N/Total patients (%)]	Asia [N/Total patients; (%)]	Other continents [N/Total patients; (%)]	*P* value
Gender				
Males	88/120 (73.3)	53/67 (79.1)	35/53 (66)	0.058
Females	32/120 (26.6)	14/67 (20.9)	18/53 (34)	0.058
Clinical features				
Headache	60/107 (56.1)	38/61 (62.3)	22/46 (47.8)	0.135
Hemiparesis	58/107 (54.2)	30/61 (49.2)	28/46 (61)	0.230
Seizure	34/107 (31.8)	25/61 (41)	9/46 (19.5)	0.018
Altered sensorium	33/107 (30.8)	15/61 (24.6)	18/46 (39)	0.107
Fever	24/107 (22.4)	16/61 (26.2)	8/46 (17.4)	0.278
Vomiting	20/107 (18.7)	11/61 (18)	9/46 (19.6)	0.840
Aphasia/dysarthria	16/107 (14.9)	7/61 (11.5)	9/46 (19.5)	0.245
Meningitis	13/109 (11.9)	9/62 (14.5)	4/47 (8.5)	0.338
Visual disturbance	12/107 (11.2)	3/61 (4.9)	9/46 (19.5)	0.017
Unsteady gait	9/107 (8.4)	5/61 (8.2)	4/46 (8.7)	1.000
Dissemination	8/112 (7.1)	1/65 (1.5)	7/47 (14.8)	0.009
History of CSOM	3/110 (2.7)	0/63 (0)	3/47 (6.3)	0.075
Sinus involvement	2/110 (1.8)	1/63 (1.6)	1/47 (2.1)	1.000
Risk of exposure to soil	40/49 (81.6)	25/33 (75.7)	15/16 (93.7)	0.238
Drug abuse	3/27 (11.1)	0/20 (0)	3/7 (42.8)	0.012
History of trauma	3/107 (2.8)	2/61 (3.3)	1/46 (2.1)	1.000
Immune status				
Immunocompetent	71/120 (59.2)	44/67 (65.7)	27/53 (51)	0.103
Immunocompromised	49/120 (40.8)	23/67 (34.3)	26/53 (49)	0.103
Immunosuppressants	6/120 (5.0)	1/67 (1.5)	5/53 (9.4)	0.047
Steroids	24/120 (20)	10/67 (14.9)	14/53 (26.4)	0.118
SOT	19/120 (15.9)	8/67 (11.9)	11/53 (20.7)	0.189
Malignancy	5/120 (4.2)	2/67 (2.9)	3/53 (5.7)	0.654
AIDS	1/120 (0.8)	1/67 (1.5)	0/53 (0)	1.000
Comorbidities				
Diabetes mellitus	10/120 (8.3)	6/67 (8.9)	4/53 (7.5)	1.000
Tuberculosis	1/120 (0.8)	1/67 (1.5)	0/53 (0)	1.000
Site /number/type of lesions				
Frontal lesion	59/111 (53.1)	39/64 (61)	20/47 (42.5)	0.055
Parietal lesion	47/111 (42.3)	32/64 (50)	15/47 (32)	0.057
Occipital lesion	11/111 (10)	5/64 (7.8)	6/47 (12.7)	0.523
Single lesion	74/110 (67.3)	46/64 (71.8)	28/46 (60.9)	0.225
Multiple lesions	36/110 (32.7)	18/64 (28.1)	18/46 (39.1)	0.225
Ring enhancing lesions	87/103 (84.5)	59/62 (95.2)	28/41 (68.3)	0.000
Management				
Surgery	101/118 (85.6)	59/66 (89.4)	42/52 (80.8)	0.185
Partial excision	41/112 (36.7)	21/62 (33.9)	20/50 (40)	0.503
Complete excision	52/112 (46.4)	32/62 (51.6)	20/50 (40)	0.221
Antifungal	90/115 (78.2)	52/64 (81.2)	38/51 (74.5)	0.384
dAmB	55/113 (48.7)	31/62 (50)	24/51 (47)	0.756
5-Flucytosine	21/113 (18.5)	7/62 (11.3)	14/51 (27.5)	0.028
Voriconazole	20/113 (17.7)	10/62 (16.1)	10/51 (19.6)	0.630
Fluconazole	16/113 (14.2)	11/62 (17.7)	5/51 (9.8)	0.228
Lipid AmB	16/113 (14.2)	5/62 (8.1)	11/51 (21.6)	0.040
Itraconazole	9/113 (7.9)	3/62 (4.8)	6/51 (11.8)	0.295
Posaconazole	4/113 (3.5)	2/62 (3.2)	2/51 (3.9)	1.000
Caspofungin	3/113 (2.7)	1/62 (1.6)	2/51 (3.9)	0.588
Ketoconazole	2/113 (1.8)	1/62 (1.6)	1/51 (1.9)	1.000
Micafungin	1/113 (0.8)	1/62 (1.6)	0/51 (0)	1.000
Surgery + Antifungal	81/115 (70.4)	49/64 (76.6)	32/51 (62.7)	0.107
Mortality	73/112 (65.2)	32/60 (53.3)	41/52 (78.9)	0.005

Abbreviations: AIDS, acquired immunodeficiency syndrome; AmB, amphotericin B; CSOM, chronic suppurative otitis media; dAmB, amphotericin B; SOT, solid organ transplant recipient.

Table 2. Antifungal susceptibility of thirteen strains of *Cladophialophora bantiana* collected at our center.

S. no	Isolate No. NCCPF	AmB	Flu	Vor	Itra	Posa	Casp	Ani	Mica
1	350012	8	16	0.06	0.03	0.06	4	2	8
2	350016	8	32	0.06	0.03	0.12	4	8	8
3	350041	0.5	32	0.25	0.12	0.12	4	4	8
4	350023	0.06	> = 64	0.25	0.12	0.03	1	8	8
5	350022	0.06	> = 64	0.06	0.12	0.03	1	8	8
6	350010	0.5	32	0.125	0.125	0.03	1	1	2
7	350047	1	8	0.06	0.250	0.03	2	1	4
8	350031	8	32	0.03	0.06	0.03	0.250	0.250	0.125
9	350032	2	16	0.06	0.125	0.03	4	4	4
10	350049	8	64	0.125	0.5	0.125	2	0.5	4
11	350052	0.5	64	0.06	0.06	0.03	2	2	4
12	350053	1	> = 64	0.06	0.250	0.03	2	0.5	2
13	350051	4	64	0.250	0.125	0.03	4	1	4

Abbreviations: AmB, amphotericin B; Ani, anidulafungin; Casp, caspofungin; Flu, fluconazole; Itra, itraconazole; Mica, micafungin; NCCPF, national culture collection of pathogenic fungi; Posa, posaconazole; Vor, Voriconazole.
Note: Data are minimum inhibitory concentrations or for the echinocandins, minimal effective concentrations, expressed as mg/l or μg/ml.

Outcome

The overall mortality was 65.2%, which was significantly high in immunosuppressed patients (77.1%) compared to immunocompetent hosts (56.3%) ($P < .022$) (Supplementary Tables 1 and 2). The survival was more (54.0%) in patients where complete excision was possible. Logistic regression analysis revealed that a complete excision (54%) was significant independent progonostic factor for survival. (OR = 3.36, 95% CI = 1.057–10.638; $P = .04$). No significant difference in survival was noted with the use of any antifungal agent or combination of antifungal agents. Multivariate analysis identified symptoms of aphasia/dysarthria (OR 12.466; 95% CI 1.237–125.674; $P = .032$), altered sensorium (OR 7.229; 95% CI 1.789–29.219; $P = .006$) and immunocompromised status (OR 3.356; 95% CI 1.040–10.829; $P = .043$) as significant predictors for mortality.

Antifungal susceptibility testing

The isolates had low minimum inhibitory concentration (MIC) against all azoles tested except fluconazole (Table 2). Six (46.2%) isolates had MIC > 1 μg/ml against amphotericin B. The MIC against echinocandins was consistently high in all isolates except one; two additional isolates had MIC of 0.5 μg/ml against anidulafungin.

Comparison of clinical characteristics of Asia patients vs other continents

The results are summarized in Table 1. The Asian patients were significantly younger (35.7 ± 15.9 years) compared to other continents (45.5 ± 19.4 years) ($P = .003$). Immunocompetent patients were more (65.7%) in Asian countries, while disseminated disease was recorded mainly from other continents. The survival was significantly more (46.7%) in Asian patients ($P = .005$), though 50% patients were treated with amphotericin B deoxycholate. The liposomal amphotericin B and 5-flucytosine uses were significantly higher (21.6% and 27.5%, respectively) in other than Asian continent. The newer azoles (voriconazole and posaconazole) and echinocandins were used in limited cases in both regions.

Discussion

C. bantiana is a highly neurotropic fungus and the presence of melanin in its cell wall possibly helps in CNS localization.[1] The taxonomy of this species has undergone many changes and has been reported earlier by several older names such as *Cladosporium trichoides*, *Cladosporium bantianum*, *Xylohypha bantiana*.[5] The first culture proven case of brain abscess due to this fungus was described in an immunocompetent American by Binford in 1952.[6] Following that report, many *C. bantiana* brain abscess cases were reported worldwide as case reports.[7–83] Majority (57.3%) of these cases was recorded from Asian continent especially from India (50%). The largest series of 10 cases over 27 years was reported from a neuroscience centre in Southern India.[69] Other Indian cases are reported as case report or couple of cases. At our center, the incidence of *C. bantiana* brain abscess was 8.1% of all fungal brain abscess cases. As the clinical course, management and outcome of the disease were not comprehensively analyzed, we reviewed all cases diagnosed and referred at our centre with all published cases in English literature. The Asian cases were compared with rest of the world. Being a review

of retrospective case reports, there is inconsistency in clinical details and follow-up. The analysis of the data is less than ideal, but it provides a description of the clinical disease pattern, usual therapy practiced, and outcome. There is a rise in number of cases reported in last decade (Fig. 1).

The males in the active age group (mean 40 ± 17.8 years) are common sufferers of the disease. The reason for this is not clear. Possibly they get the exposure while working in farming land, as this fungus is believed to inhabit plant material and soil. This fungus can tolerate and grow at higher temperature (>39°C). As *C. bantiana* brain abscess is more prevalent in Asian countries, it is tempting to believe that the high temperature of tropical region of these countries allows this fungus to thrive. A detailed environmental survey for this fungus in this region is essential to understand exact epidemiology of the disease.

The infection is seen both in apparently immunocompetent and immunocompromised hosts with slight predominance (59.2%) in the former group. The mode of entry of *C. bantiana* is not clearly understood. As the lesions are seen in many parts of brain including frontal (53.1%), parietal (42.3%), occipital (10%) regions, the agent possibly enters brain through bloodstream from an innocuous site of infection in lung or subcutaneous traumatic inoculation site.

The early diagnosis of the disease is a formidable challenge due to its rarity and lack of specific symptoms and signs of the disease. The mean duration of symptoms before diagnosis was 115 days in this review. The common clinical presentations of *C. bantiana* brain abscess mimic space occupying lesion (SOL) with headache, fever, altered sensorium, hemiparesis, aphasia/dysarthria, and vomiting. It is difficult to diagnose or differentiate the disease from other common SOL like malignancy or tuberculoma. The lesions in the brain can be single or multiple involving the grey and white matter of cerebral cortex. Rarely the lesion may be found in choroid plexus, thalamus, basal ganglia, and cerebellum. Though a rise in protein in CSF was noted, it did not help in suspecting the disease. The disease is equally prevalent in immunocompetent and immunocompromised hosts. Therefore, until a specific biomarker or serological test is developed for screening, a strong clinical suspicion is required for early diagnosis, especially in Asian countries. Any peripheral localization of infection in subcutaneous tissue or lung may help in diagnosis. The increase in number of cases diagnosed from Asian countries in the last four years indicates the possibility of an increased awareness of the disease in this region.

There is no standard therapy for *C. bantiana* brain abscess. Recently ESCMID and ECMM joint guideline recommended complete excision of encapsulated abscess combined with antifungal mono or combination therapy.[84] During the last century, most of the patients were treated with amphotericin B deoxycholate and 5-flucytosine. Lipid preparations of amphotericin B were used infrequently and its use in Asian countries was rare possibly due to high cost of the drug. Fluconazole and itraconazole were used in occasional patients. Fluconazole crosses blood brain barrier well, but it has little activity against *C. bantiana*.[2,85] Fluconazole MIC was high (range $8 \geq 64$ μg/ml) in our 13 isolates tested. Comparatively itraconazole has better activity against *C. bantiana*, but it penetrates poorly into the CSF.[86] However, itraconazole can concentrate in brain tissue.[87] 5-flucytosine has *in vitro* activity against dematiaceous fungi including *C. bantiana* and can penetrate the central nervous system (CNS).[88,89] This drug is prescribed in combination with amphotericin B and never used alone. The newer agents, voriconazole and posaconazole have a good *in vitro* susceptibility against *C. bantiana* as noted in our isolates. The *in vivo* outcome cannot be commented, as those drugs were used in few clinical cases. Voriconazole penetrates central nervous system well, whereas posaconazole has been found to be useful in invasive model of CNS phaeohyphomycosis.[90] Echinocandins penetrate CSF poorly; the five patients treated with this drug in this series had little success. The susceptibility testing of all our 13 isolates showed high MICs against all three echinocandins. However, echinocandin is recommended in combination therapy with azole and flucytosine when surgery is not possible.[84] The reason for this is not clear. Terbinafine has good *in vitro* activity against dematiaceous fungi, but the drug was not used in any patient with *C. bantiana* abscess.[91] None of the drugs used in this series against *C. bantiana* brain abscess was found to be independently associated with improved outcome, though voriconazole and posaconazole use was marginally supported by ESCMID and ECMM joint guideline.[84] The mortality of *C. bantiana* brain abscess was high at 65.2%. Only complete excision of lesion in immunocompetent host was found to be significantly associated with better outcome. Several issues like delay in diagnosis, variable *in vitro* susceptibility of the fungus to antifungal drug, and the site of lesion play important role in poor outcome in the disease. Studies are required for successful early diagnostic test and effective combination of antifungal drugs to get success against this refractive infection.

In conclusion, *C. bantiana* brain abscess is an emerging infection in Asian countries, especially India. The disease has been observed with relative high frequencies in young, immunocompetent individuals from rural background. The disease is diagnosed only by conventional techniques including biopsy and culture, which are insensitive and take long turnaround time. Triazoles other than fluconazole have good *in vitro* activity against the fungus. A complete early excision of the lesion with

effective antifungal drug may improve the outcome of these cases.

Acknowledgments

We thank Dr Umabala Pamidimukkala, Dr Bansidhar Tarai, Dr Anita Sharma, Dr Sukanya R, Dr Archana Asokan, Dr Bhavin Kapadia, Dr Bhupendra Patel, Dr Rajeshwari Narayan, and Dr Ratna Rao for information on the clinical cases.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

Supplementary material

Supplementary material is available at *Medical Mycology* online (http://www.mmy.oxfordjournals.org/).

References

1. Revankar SG, Sutton DA, Rinaldi MG. Primary central nervous system phaeohyphomycosis: a review of 101 cases. *Clin Infect Dis* 2004; **38**: 206–216.
2. Ajantha GS, Kulkarni RD. *Cladophialophora bantiana*, the neurotropic fungus – a mini review. *J Clin Diagn Res* 2011; **5**: 1301–1306.
3. Al-Abdely HM. Phaeohyphomycosis: A dark question mark in clinical disease. *J Invasive Fungal Infect* 2009; **3**: 82–88.
4. *Reference method for broth dilution antifungal susceptibility testing of filamentous fungi: approved standard-second edition*. CLSI document M38-A2. Clinical and Laboratory Standards Institute, Wayne, PA: CLSI, 2008.
5. Matsumoto T, Ajello L. Agents of phaeohyphomycosis. In: Ajello L, Hay RJ, eds. *Medical mycology*. 9th ed. London: Arnold, 1998, 503–524.
6. Binford CH, Thompson RK, Gorham ME. Mycotic brain abscess due to *Cladosporium trichoides*, a new species; report of a case. *Am J Clin Pathol* 1952; **22**: 535–542.
7. King AB, Collette TS. Brain abscess due to *Cladosporium trichoides*; report of the second case due to this organism. *Bull Johns Hopkins Hosp* 1952; **91**: 298–305.
8. Bobra S. Mycotic abscess of the brain probably due to *Cladosporium trichoides*: Report of the fifth case. *Can Med Ass J* 1958; **79**: 657–659.
9. Horn IH, Wilansky DL, Harland WA et al. Neurogenic hypernatremia with mycotic brain granulomas due to *Cladosporium trichoides*. *Can Med Assoc J* 1960; **83**: 1314–1317.
10. Riley O, Mann SH. Brain abscess caused by *Cladosporium trichoides*. *Am J Clin Pathol* 1960; **33**: 525–531.
11. Symmers WS. A case of cerebral chromoblastomycosis (cladosporiosis) occurring in britain as a complication of polyarteritis treated with cortisone. *Brain* 1960; **83**: 37–51.
12. Watson KC. Cerebral chromoblastomycosis. *J Pathol Bacteriol* 1962; **84**: 233–237.
13. Bagchi A, Aikat BK, Barua D. Granulomatous lesion of the brain produced by *Cladosporium trichoides*. *J Indian Med Assoc* 1962; **38**: 602–604.
14. Duque O. Meningo-encephalitis and brain abscess caused by *Cladosporium* and *Fonsecaea*. Review of the literature, report of two cases, and experimental studies. *Am J Clin Pathol* 1961; **36**: 505–517.
15. Dastur HM, Chaukar AP, Rebello MD. Cerebral chromoblastomycosis due to *Cladosporium trichoides (bantianum)*. I. (A review and case report). *Neurol India* 1966; **14**: 1–5.
16. Musella RA, Collins GH. Cerebral chromoblastomycosis. Case report. *J Neurosurg* 1971; **35**: 219–222.
17. Bennett JE, Bonner H, Jennings AE et al. Chronic meningitis caused by *Cladosporium trichoides*. *Am J Clin Pathol* 1973; **59**: 398–407.
18. Crichlow DK, Enrile FT, Memon MY. Cerebellar abscess due to *Cladosporium trichoides (bantianum)*: case report. *Am J Clin Pathol* 1973; **60**: 416–421.
19. Middleton FG, Jurgenson PF, Utz JP et al. Brain abscess caused by *Cladosporium trichoides*. *Arch Intern Med* 1976; **136**: 444–448.
20. Brown JW, Nadell J, Sanders CV et al. Brain abscess caused by *Cladosporium trichoides* (*bantianum*): a case with paranasal sinus involvement. *South Med J* 1976; **69**: 1519–1521.
21. Hironaga M, Watanabe S. Cerebral phaeohyphomycosis caused by *Cladosporium bantianum*: a case in a female who had cutaneous alternariosis in her childhood. *Sabouraudia* 1980; **18**: 229–235.
22. Kim RC, Hodge CJ, Lamberson HV et al. Traumatic intracerebral implantation of *Cladosporium trichoides*. *Neurology* 1981; **31**: 1145–1148.
23. Sandhyamani S, Bhatia R, Mohapatra LN et al. Cerebral cladosporiosis. *Surg Neurol* 1981; **15**: 431–434.
24. Wilson E. Cerebral abscess caused by *Cladosporium bantianum*. Case report. *Pathology* 1982; **14**: 91–96.
25. Seaworth BJ, Kwon-Chung KJ, Hamilton JD et al. Brain abscess caused by a variety of *Cladosporium trichoides*. *Am J Clin Pathol* 1983; **79**: 747–752.
26. Chandramukhi A, Ramadevi MG, Shankar SK. Cerebral cladosporiosis–a neuropathological and microbiological study. *Clin Neurol Neurosurg* 1983; **85**: 245–253.
27. Salem FA, Kannangara DW, Nachum R. Cerebral chromomycosis. *Arch Neurol* 1983; **40**: 173–174.
28. Küllü S, Onol B, Kuştimur S et al. Cerebral cladosporiosis. *Surg Neurol* 1985; **24**: 437–440.
29. Bhatia R, Tandon P, Misra NK. Inflammatory lesions of the basal ganglia and thalamus: review of twenty-one cases. *Neurosurgery* 1986; **19**: 983–988.
30. Banerjee U, Mohapatra AK, Sarkar C et al. Cladosporiosis (cerebral phaeohyphomycosis) of brain—a case report. *Mycopathologia* 1989; **105**: 163–166.
31. Heney C, Song E, Kellen A et al. Cerebral phaeohyphomycosis caused by *Xylohypha bantiana*. *Eur J Clin Microbiol Infect Dis* 1989; **8**: 984–988.
32. Aldape KD, Fox HS, Roberts JP et al. *Cladosporium trichoides* cerebral phaeohyphomycosis in a liver transplant recipient. Report of a case. *Am J Clin Pathol* 1991; **95**: 499–502.

33. Goel A, Satoskar A, Desai AP et al. Brain abscess caused by *Cladosporium trichoides*. *Br J Neurosurg* 1992; **6**: 591–593.
34. Sekhon AS, Galbraith J, Mielke BW et al. Cerebral phaeohyphomycosis caused by *Xylohypha bantiana*, with a review of the literature. *Eur J Epidemiol* 1992; **8**: 387–390.
35. Dar L, Singh S, Banerjee U et al. Cerebral phaeohyphomycosis caused by *Xylohypha bantiana*. *Indian J Med Microbiol* 1993; **11**: 148–150.
36. Nadkarni TD, Goel A, Shenoy A et al. *Cladosporium bantianum* (trichoides) infection of the brain. *J Postgrad Med* 1993; **39**: 43–44.
37. Palaoglu S, Sav A, Basak T et al. Cerebral phaeohyphomycosis. *Neurosurgery* 1993; **33**: 894–897.
38. Imwidthaya P. Systemic fungal infections in Thailand. *J Med Vet Mycol* 1994; **32**: 395–399.
39. Lirng JF, Tien RD, Osumi AK et al. Cerebral phaeohyphomycosis complicated with brain abscess: a case report. *Zhonghua Yi Xue Za Zhi* 1995; **55**: 491–495.
40. Mukherji SK, Castillo M. Cerebral phaeohyphomycosis caused by *Xylohypha bantiana*: MR findings. *AJR Am J Roentgenol* 1995; **164**: 1304–1305.
41. Rossmann SN, Cernoch PL, Davis JR. Dematiaceous fungi are an increasing cause of human disease. *Clin Infect Dis* 1996; **22**: 73–80.
42. Buxi TB, Prakash K, Vohra R et al. Imaging in phaeohyphomycosis of the brain: case report. *Neuroradiology* 1996; **38**: 139–141.
43. Emmens RK, Richardson D, Thomas W et al. Necrotizing cerebritis in an allogeneic bone marrow transplant recipient due to *Cladophialophora bantiana*. *J Clin Microbiol* 1996; **34**: 1330–1332.
44. Gupta SK, Manjunath-Prasad KS, Sharma BS et al. Brain abscess in renal transplant recipients: Report of three cases. *Surg Neurol* 1997; **48**: 284–287.
45. Salama AD, Rogers T, Lord GM et al. Multiple *Cladosporium* brain abscesses in a renal transplant patient: aggressive management improves outcome. *Transplantation* 1997; **63**: 160–162.
46. Walz R, Bianchin M, Chaves ML et al. Cerebral phaeohyphomycosis caused by *Cladophialophora bantiana* in a Brazilian drug abuser. *J Med Vet Mycol* 1997; **35**: 427–431.
47. Freitas A, Pedral-Sampaio D, Espinheira Nogueira L et al. *Cladophialophora bantiana* (Previously *Cladosporium trichoides*): First report of a case in Brazil. *Braz J Infect Dis* 1997; **1**: 313–316.
48. Arunkumar MJ, Rajshekhar V, Chandy MJ et al. Management and outcome of brain abscess in renal transplant recipients. *Postgrad Med J* 2000; **76**: 207–211.
49. Sood P, Dogra V, Thakur A et al. Brain abscess due to *Xylohypha bantiana*. *Scand J Infect Dis* 2000; **32**: 708–709.
50. Vyas MC, Joshi YR, Bhargava N et al. Cerebral chromoblastomicosis—a rare case report of cerebral abscess and brief review of literature—a case report. *Indian J Pathol Microbiol* 2000; **43**: 81–85.
51. Banerjee TK, Patwari AK, Dutta R et al. *Cladosporium bantianum* meningitis in a neonate. *Indian J Pediatr* 2002; **69**: 721–723.
52. Shields GS, Castillo M. Myelitis caused by *Cladophialophora bantiana*. *AJR Am J Roentgenol* 2002; **179**: 278–279.
53. Keyser A, Schmid FX, Linde HJ et al. Disseminated *Cladophialophora bantiana* infection in a heart transplant recipient. *J Heart Lung Transplant* 2002; **21**: 503–505.
54. Raut A, Muzumdar D, Narlawar R et al. Cerebral abscess caused by *Cladosporium bantianum* infection—case report. *Neurol Med Chir* 2003; **43**: 413–415.
55. Alhabib KF, Bryce EA. *Xylohypha bantiana* multiple brain abscesses in a patient with systemic lupus erythematosus. *Can J Infect Dis* 2003; **14**: 119–120.
56. Silveira ER, Resende MA, Mariano VS et al. Brain abscess caused by *Cladophialophora (Xylohypha) bantiana* in a renal transplant patient. *Transpl Infect Dis* 2003; **5**: 104–107.
57. Lee YM, Tambyah PA, Lee KH et al. Successful treatment of *Xylohypha bantiana* brain abscess mimicking invasive cerebral aspergillosis in a liver transplant recipient. *J Infect* 2003; **47**: 348–351.
58. Trinh JV, Steinbach WJ, Schell WA et al. Cerebral phaeohyphomycosis in an immunodeficient child treated medically with combination antifungal therapy. *Med Mycol* 2003; **41**: 339–345.
59. Fica A, Diaz M-C, Luppi M et al. Unsuccessful treatment with voriconazole of a brain abscess due to *Cladophialophora bantiana*. *Scand J Infect Dis* 2003; **35**: 892–893.
60. Levin TP, Baty DE, Fekete T et al. *Cladophialophora bantiana* brain abscess in a solid-organ transplant recipient: Case report and review of the literature. *J Clin Microbiol* 2004; **42**: 4374–4378.
61. Singh S, Singh P, Sarkar C et al. Fungal granuloma of the brain caused by *Cladosporium bantianum*–a case report and review of literature. *J Neurol Sci* 2005; **228**: 109–112.
62. Lyons MK, Blair JE, Leslie KO. Successful treatment with voriconazole of fungal cerebral abscess due to *Cladophialophora bantiana*. *Clin Neurol Neurosurg* 2005; **107**: 532–534.
63. Deb S, Khan AK, Debasish B et al. Intracranial necrotizing granuloma caused by *Cladophialophora bantiana*. *Neurol India* 2005; **53**: 335–336.
64. Delfino D, De Hoog S, Polonelli L et al. Survival of a neglected case of brain abscess caused by *Cladophialophora bantiana*. *Med Mycol* 2006; **44**: 651–654.
65. Pardo F, Ferrer E, Romero PA et al. Cerebral phaeiohyphomycosis due to *Cladophialophora bantiana*. *Enferm Infecc Microbiol Clin* 2006; **24**: 593–594.
66. Adeyemi OA, Lie O, Bernstein R et al. Woman with multiple brain abscesses. *Clin Infect Dis* 2007; **45**: 1351–1352.
67. Jayakeerthi SR, Dias M, Nagarathna S et al. Brain abscess due to *Cladophialophora bantiana*. *Indian J Med Microbiol* 2004; **22**: 193–195.
68. Takei H, Goodman JC, Powell SZ. Cerebral phaeohyphomycosis caused by *Cladophialophora bantiana* and *Fonsecaea monophora*: report of three cases. *Clin Neuropathol* 2007; **26**: 21–27.
69. Garg N, Devi IB, Vajramani GV et al. Central nervous system cladosporiosis: an account of ten culture-proven cases. *Neurol India* 2007; **55**: 282–288.
70. Harrison DK, Moser S, Palmer CA. Central nervous system infections in transplant recipients by *Cladophialophora bantiana*. *South Med J* 2008; **101**: 292–296.

71. Garzoni C, Markham L, Bijlenga P et al. *Cladophialophora bantiana*: a rare cause of fungal brain abscess. Clinical aspects and new therapeutic options. *Med Mycol* 2008; **46**: 481–486.
72. Borkar S, Sharma MS, Rajpal G et al. Brain abscess caused by *Cladophialophora bantiana* in an immunocompetent host: need for a novel cost-effective antifungal agent. *Indian J Med Microbiol* 2008; **26**: 271–274.
73. George IA, Mathews MS, Karthik R et al. Fatal cerebral abscess caused by *Cladophialophora bantiana*. *J Assoc Physicians India* 2008; **56:** 470–472.
74. Lakshmi V, Padmasri V, Umabala P et al. Cerebral phaeohyphomycosis due to *Cladophialophora bantiana*. *Indian J Med Microbiol* 2008; **26**: 392–395.
75. Rattanaumpawan P, Tantimavanich S, Tiengrim S et al. Disseminated *Cladophialophora bantiana* infection in an idiopathic thrombocytopenic purpura patient: a case report. *Mycoses* 2011; **54**: 544–548.
76. Revankar SG. *Cladophialophora bantiana* brain abscess in an immunocompetent patient. *Can J Infect Dis Med Microbiol* 2011; **22**: 149–150.
77. Huang WM, Fan YM, Li W et al. Brain abscess caused by *Cladophialophora bantiana* in China. *J Med Microbiol* 2011; **60**: 1872–1874.
78. Aher A, Rastogi V. A case of cerebral abscess due to *Cladophialophora bantiana*. *J Microbiol Infect Dis* 2012; **2**: 171–173.
79. Agrawal A, Shanthi V, Murali Mohan KV et al. *Cladophialophora bantiana* brain abscess masquerading cerebral tuberculoma in an immunocompetent host. *Rom Neurosurg* 2014; **21**: 75–79.
80. Suri P, Chhina DK, Kaushal V et al. Cerebral Phaeohyphomycosis due to *Cladophialophora bantiana*—A Case Report and Review of Literature from India. *J Clin Diagn Res* 2014; **8**: 1–5.
81. Sladekova M, Poczova M, Gaspar M et al. First case of systemic phaeohyphomycosis due to *Cladophialophora bantiana* in Slovakia. *JMM Case Reports* 2014; **1**: e002659.
82. Husova L, Kocmanova I, Zampachova V et al. *Cladophialophora bantiana* in a liver transplant recipient. *Surg Infect* 2015; **16**: 211–212.
83. Mansour A, Jordan K. Disseminated *Cladophialophora bantiana* disease in a patient with prediabetes. *BMJ Case Rep* 2014; doi:10.1136/bcr-2014–206426.
84. Chowdhary A, Meis JF, Guarro J et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. *Clin Microbiol Infect* 2014; **20**(Suppl. 3): 47–75.
85. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev* 2010; **23**: 858–883.
86. Sharkey PK, Graybill JR, Rinaldi MG et al. Itraconazole treatment of phaeohyphomycosis. *J Am Acad Dermatol* 1990; **23**(3 Pt 2): 577–586.
87. Groll AH, Piscitelli SC, Walsh TJ. Clinical pharmacology of systemic antifungal agents: a comprehensive review of agents in clinical use, current investigational compounds, and putative targets for antifungal drug development. *Adv Pharmacol* 1998; **44:** 343–500.
88. Francis P, Walsh TJ. Evolving role of flucytosine in immunocompromised patients: new insights into safety, pharmacokinetics, and antifungal therapy. *Clin Infect Dis* 1992; **15**: 1003–1018.
89. Dixon DM, Polak A. *In vitro* and *in vivo* drug studies with three agents of central nervous system phaeohyphomycosis. *Chemotherapy* 1987; **33**: 129–140.
90. Al-Abdely HM, Najvar L, Bocanegra R et al. SCH 56592, amphotericin B, or itraconazole therapy of experimental murine cerebral phaeohyphomycosis due to *Ramichloridium obovoideum* ('*Ramichloridium mackenziei*'). *Antimicrob Agents Chemother* 2000; **44**: 1159–1162.
91. McGinnis MR, Pasarell L. *In vitro* evaluation of terbinafine and itraconazole against dematiaceous fungi. *Med Mycol* 1998; **36**: 243–246.