Case Report

Survival of a neglected case of brain abscess caused by *Cladophialophora bantiana*

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*Cladophialophora bantiana* is an uncommon fungus related to the black yeasts which causes, if untreated, mostly fatal cerebral infections in immunosuppressed and competent patients. We report a case of a patient who survived a recurrent cerebral abscess caused by *C. bantiana* despite delayed and apparently inappropriate therapy.

**Keywords** black yeast, *Cladophialophora bantiana*, cerebral abscess, brain surgery, fluconazole

Introduction

Brain abscesses are but one of the characteristic pathologies caused by the highly virulent, melanized fungus *Cladophialophora bantiana*. The majority of the patients die despite early recognition of the fungus as the causative agent and surgical intervention and/or pharmacological treatment with different antifungal drug combinations [1]. Although several constitutive factors are believed to play a role in its pathogenesis, the disease frequently affects immunocompetent, otherwise healthy patients [2]. Cerebral infection is generally fatal [2] in those patients who do not receive any treatment and, as a result, cases involving delayed or inappropriate antifungal therapy have poor prognoses.

We describe the course of events of a patient with a cerebral abscess, who did not receive any antifungal drug for a long period of time but was eventually treated successfully through repeated surgical interventions followed by therapy with low doses of fluconazole. The patient was a drug abuser at the time of admission to the hospital and i.v. use of drugs has already been reported as a possible risk factor [3].

Case report

A 29-year-old white male born and living in Messina (Italy) was admitted to hospital for the first time in January 2003. On admission the patient complained of headache and right hemiparesis. While he was a drug abuser, there was no history of relevant disorders. Hematological values were normal and the analysis of humoral and cellular immunity showed a slight reduction of IgM levels (28 mg/dl; normal values 40–230 mg/dl), normal complement fractions C4 and C3, a slight reduction of the CD4+/CD8+ ratio (1.1; normal values 1.4–2.8), and normal total CD4+ and CD8+ counts. The HIV test as well as blood cultures for bacteria were negative. A post contrast magnetic resonance (NMR) of the brain revealed a 2 cm wide abscess in the left parietal region (Fig. 1 A).

The patient refused surgery and left the hospital voluntarily in February 2003. However, in June 2003 a convulsive crisis forced him to return to hospital, at which time computed tomography (CT) showed progression of his brain lesion. Empirical antibiotic

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therapy with ceftazidime was administered, but he again refused surgery and left the hospital of his own volition in July 2003. Eighteen days later, episodes of severe headaches caused him to again be admitted to hospital and a NMR confirmed the presence of the lesion in the left parietal cerebral region. Finally, in August 2003 the patient underwent surgical intervention with excision of the abscess. Histology revealed the presence of a granulomatous reaction with necrotic lesions and numerous giant cells along the rim of a capsule surrounding the abscess, but no hyphal elements were observed at that time.

Cultures for bacteria were negative. The patient was treated with ceftazidime and discharged from the hospital. Subsequently, the abscess relapsed and was surgically removed twice, in November 2003 and March 2004. After the last operation a sample of pus was sent to the mycology laboratory for culture and after 15 days of incubation at 30°C, a black velvety mold was isolated on Sabouraud's dextrose agar. Before definitive identification of the etiological agent, empirical treatment was begun with low dose fluconazole (100 mg/day). The patient was discharged by mid-March 2004, continuing therapy as an outpatient for 21 days. A CT scan performed after the third operation of April 2004 did not reveal the presence of any abscess in the brain parenchyma.

The initial isolate was subcultured, under full safety precautions, on Mycosel agar containing cycloheximide and cloramphenicol. Its growth at 42°C and microscopic examination of a potato dextrose agar slide culture resulted in its presumptive identification as *Cladophialophora bantiana*. It was deposited as CBS 118679 and definitively identified as *C. bantiana* on the basis of a species-specific SSU-intron located at position 1768 [4] and by ITS rDNA sequencing.

Confirmation of *C. bantiana* as the causative agent resulted in a retrospective histological analysis of the frozen excised mass stored at the Department of Human Pathology of the University of Messina. Hematoxylin-eosin stained sections clearly showed the presence of hyphal and conidial elements compatible with *C. bantiana* morphology (Fig. 2).

Antifungal susceptibility testing was performed for amphotericin B, fluconazole, itraconazole, ketoconazole, and voriconazole according to the guidelines for filamentous fungi proposed by the National Committee for Clinical Laboratory Standards (NCCLS) [5]. The drugs were provided as pure powders by the United States Pharmacopeia (USP) except for voriconazole (personal gift). The isolate was susceptible to voriconazole, itraconazole and ketoconazole (Table 1). It is difficult to interpret MICs data for amphotericin B and fluconazole. According to the NCCLS, filamentous fungi isolates with MICs above 2 μg/ml for amphotericin B or above 64 μg/ml for fluconazole, are considered resistant and have been associated with treatment failure. Actually there are no established data indicating breakpoints for molds. If one applies the fluconazole breakpoint derived from yeast infections, this isolate could be defined as 'susceptible-dependent-upon-dose'. In view of the in vitro susceptibility value (Table 1), the low-dose fluconazole treatment employed with this patient had perhaps little effect on the outcome of the infection.
Table 1  Antimycotic susceptibility of Cladophialophora bantiana, isolated from the brain (and reference isolates) according to the broth microdilution method after the NCCLS M38-A protocol

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>C. bantiana ATCC 204304</th>
<th>A. flavus ATCC 204304</th>
<th>C. parapsilosis ATCC 22019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>32.0</td>
<td>64.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>0.5</td>
<td>4.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.5</td>
<td>1.0</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Aspergillus flavus ATCC 204304 and Candida parapsilosis ATCC 22019 were used as reference isolate and quality control strain respectively.

The MIC values were in agreement with those published for C. bantiana [6] with the exception of fluconazole which was not included in the study. Repeated NMR scans in October 2004 and April 2005 (Fig. 1B) showed no relapse. The patient was considered cured and no further treatment was given.

Discussion

Cladophialophora bantiana is a melanized fungus with predilection for the central nervous system. While its natural habitat is currently unknown [7], it would appear to be widely distributed [2]. About two-thirds of infections occur in immunocompetent patients and the mortality rate, independent of the immune status of the patients, is over 70% [1,2,8]. The present case concerned a cerebral abscess localized in the parenchyma, similar to previous cases as recently described in a review [7]. Although our patient had no remarkable history of disease or immunosuppression, two possible risk factors at the time of hospital admission, i.e., i.v. drug use and a job in which he was regularly exposed to dust (car body repair), may have contributed to an intravenous or a respiratory route of infection, respectively. Compared to reported cases, the one described here is characterized by prolonged survival of the patient despite apparent absence of appropriate pharmacological therapy. At present no standard therapy against melanized molds is available. Combinations of different antifungals and complete resection of the abscess are believed to improve the survival rate [1,2,9]. In this case, two surgical interventions performed prior to the identification of C. bantiana did not prevent recurrence of the abscess at the same site. Once the etiologic agent was identified after the third surgical intervention, the patient was treated for 21 days with a low dose regimen of fluconazole. Since this antifungal is normally considered ineffective against filamentous molds, it has rarely been used for C. bantiana infections [10,11], despite its good penetration into the central nervous system. However, surprisingly, the abscess did not relapse after fluconazole treatment.

It is generally agreed that surgical removal alone is unlikely to result in complete resolution of a C. bantiana infection [2]. However, encapsulated lesions such as the one presented here are associated with a better prognosis compared to non-granulomatous, poorly encapsulated ones [8]. In addition it is unclear whether the results of in vitro susceptibility tests have predictive in vivo value because of the limited number of infections studied [12].

In conclusion, this case emphasizes the insufficiency of a single surgical intervention to eradicate the fungal infection, as demonstrated by the recurrence of the lesion. No less than three operations were necessary to obtain a cure. The possible positive effects of antifungal therapy as an adjuvant to surgery is still unclear as the use of fluconazole, to which the fungus could be resistant judging from antifungal susceptibility data, proved to be successful at least in one other case [11]. Since C. bantiana is a highly infective pathogen, and since the central nervous system infections that it causes have a high mortality rate, it is our opinion that it should be handled in a BSL-3 facility.

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