Case Report

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Brain abscess caused by *Cladophialophora bantiana* in China

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A case of a 38-year-old male farmer with a brain abscess caused by *Cladophialophora bantiana* is described. He had a 2 year history of non-insulin-dependent diabetes and myelodysplastic syndrome. A cranial computed tomography scan demonstrated a hypodense ring lesion with peripheral oedema and a midline shift in the left frontal lobe. A darkly pigmented mould was isolated from the brain abscess. The isolate was identified as *C. bantiana* based on its morphological features and DNA sequence analysis. The patient was unresponsive to burr hole aspiration and irrigation, as well as liposomal amphotericin B infusion, and died after discharge from the hospital. This is believed to be the first case of a cerebral abscess due to *C. bantiana* in China.

Introduction

Cladophialophora bantiana, formerly called ‘*Cladosporium trichoides*’, ‘*Cladosporium bantianum*’, ‘*Xylohypha bantiana*’ and ‘*Xylohypha emmonsii*’, is one of the most common pathogens that causes cerebral phaeohyphomycosis (Levin *et al.*, 2004; Li & de Hoog, 2009). Although some authors state that *C. bantiana* can be isolated from soil, decaying lumber and vegetation, and the brick walls (of a warehouse) (Emmens *et al.*, 1996; Shields & Castillo, 2002), only one such strain (CBS 647.96) has been recovered from sawdust, and the environmental habitat of the species is basically unknown (Badali *et al.*, 2010). Binford and colleagues described the first culture-proven case of cerebral phaeohyphomycosis due to *C. bantiana* in 1952 (Revankar *et al.*, 2004). Of the 101 cases of primary central nervous system (CNS) phaeohyphomycosis between 1966 and 2002, *C. bantiana* was isolated from 48 (48 %) cases, and was the most common species (Revankar *et al.*, 2004). To date more than 70 cases of *C. bantiana*-induced infections have been reported (Li & de Hoog, 2009). We describe herein what is believed to be the first case of cerebral abscess caused by *C. bantiana* in China.

Case report

A 38-year-old male farmer was admitted to our hospital with faciobrachial tonic seizure and right-sided hemiparesis in March 2008. The seizure was accompanied with a

loss of consciousness lasting for 4–5 min, and recurred for 45 days. Progressive weakness of the right limbs and occasional vomiting appeared 30 days later. No history of fever, dizziness, headache or urinal and faecal incontinence was recorded. The patient had a 2 year history of non-insulin-dependent diabetes and myelodysplastic syndrome. He was diagnosed as having an abscess of the left frontal lobe by magnetic resonance imaging, and was treated ineffectively in another hospital. Physical examination revealed that his vital signs and consciousness were normal, meningeal irritation sign was positive, and muscle strength of the right limbs was grade III. Laboratory studies showed that erythrocyte, leukocyte and platelet counts were 3.4×10^{12} erythrocytes l^{-1} , 3.14×10^9 leukocytes l^{-1} and 65×10^9 platelets l^{-1} , respectively. His blood sugar level was 12 mmol l^{-1} . Rapid plasma reagent and human immunodeficiency virus antibody tests were negative, but a *Treponema pallidum* passive particle agglutination assay was positive. The findings of chest roentgenogram and electrocardiogram were normal. The patient was unresponsive to the empirical antibiotic and symptomatic treatment for 12 days. A cranial computed tomography (CT) scan without contrast demonstrated a hypodense ring lesion with peripheral oedema and mild mass effect in the left frontal lobe (Fig. 1) on hospital day 9. A single burr hole aspiration was performed 3 days later, with repeated irrigation with gentamicin and normal saline [320 mg gentamicin in 500 ml (0.9%) NaCl]. A potassium hydroxide (KOH) mount of the purulent aspirate showed fungal elements, but bacteriological examination was negative, suggestive of fungal brain abscess. The patient exhibited aphasia, dysphoria and exacerbation of the right limb weakness on hospital day 15, and a repeat brain CT

Abbreviations: CNS, central nervous system; CT, computed tomography; ITS, internal transcribed spacer.

The GenBank/EMBL/DBJ accession number for the ITS sequence of *Cladophialophora bantiana* is GQ258793.

Fig. 1. Cranial CT scan demonstrating a hypodense ring lesion with peripheral oedema and a midline shift in the left frontal lobe. Magnification $\times 1.00$.

showed no reduction of the ring-enhancing lesion in the left frontal lobe with peripheral oedema and midline shift. Liposomal amphotericin B was started at a dose of 50 mg per day on hospital day 16 and increased doubly after 2 days, but ceased after 8 days due to lack of money. However, no clinical improvement was noted thereafter. The patient presented with convulsion and coma on hospital day 22, and underwent another three aspirations and intracavitary administrations of liposomal amphotericin B (2.5 mg) on hospital days 24, 25 and 27. A darkly pigmented mould was isolated from the brain abscess, and a KOH mount of the pus was still positive on hospital day 24. The patient continued to suffer mild coma, and developed hyperpyrexia, hyperspasmia, hematemesis and low blood pressure on hospital day 29. The family requested that all treatments be discontinued because of the unresponsive therapy and economic burden. The patient died after discharge from the hospital.

KOH preparation of the purulent aspirate before and after amphotericin B treatment showed numerous brown septate, branching or irregular swollen hyphae, with a few lateral or terminal chlamydospores. Two aspirated pus specimens were cultured on Sabouraud dextrose agar (SDA) without antibiotics at 27 °C, and produced greyish black velvety colonies after 2 weeks. The strain was subcultured on an SDA plate at 27 °C. A greyish black colony began to appear on day 5, and attained diameters of 0.5, 1.0, 1.2 and 1.9 cm on day 5, 7, 9 and 14, respectively. Its colour turned from grey to black, and its surface gradually became velvety and developed folds at the centre with the increasing incubation time. The velvety surface of

the colony showed irregular central folds, giving a button-like appearance, with the radiation of peripheral black hyphae after 2 weeks, while the reverse was nearly black. A slide culture of the mould was incubated at 27 °C, and observed daily after 48 h. The brown septate conidiophores observed were short or poorly differentiated. The single-celled conidia were smooth walled and ellipsoidal or pear-shaped, without pigmented hila, and formed sparsely branched, long chains with an acropetal arrangement (Fig. 2). The fungus grew slowly at 42 °C, with the optimal growth temperature being 35–37 °C, but failed to grow above 43 °C or below 8 °C. The isolate grew after 48 h exposure to 2.5 and 5 % KOH solution, but failed to grow after treatment with 10 % KOH solution. A gelatin liquefaction test showed an absence of proteolytic activity. The isolated fungus was sent to the Institute of Microbiology, Chinese Academy of Sciences, Beijing, China, for genetic confirmation of the identification. The internal transcribed spacer (ITS) region of the fungal rRNA gene was amplified using ITS1 (5'-GTC GTA ACA AGG TTT CCG TAG GTG-3') and ITS4 (5'-TCC TCC GCT TAT TGA TAT GC-3'), followed by direct sequencing of the product. The ITS sequence (585 bp) of the isolate (GenBank accession number GQ258793) showed 100 % homology to *C. bantiana* sequences in GenBank, e.g. UTHSC94-986 (AF131079), CBS102586 (EU103990), CBS173.52 (EU103989), CBS117890 (EU137279) and CBS100436 (AY857513). The isolate was identified as *C. bantiana* based on the morphological features and the DNA sequence analysis.

Discussion

C. bantiana is a highly neurotropic dematiaceous fungus that can cause human brain abscess. The predisposing factors include organ transplantation, glucocorticoid treatment, neutropenia, diabetes mellitus, direct inoculation, ocular injury, intravenous drug abuse etc. (Levin *et al.*, 2004;

Fig. 2. Microscopic examination of the culture mounts revealing sparsely branched, long chains of conidia (10 % KOH; original magnification $\times 400$).

Revankar *et al.*, 2004; Garzoni *et al.*, 2008), whereas the infective routes include haematogenous dissemination from a primary invasion site (mostly the lung), direct brain inoculation, and paranasal sinus and ear infection (Emmens *et al.*, 1996; Sood *et al.*, 2000; Garzoni *et al.*, 2008). Occupational exposure was very important because 44 % of patients had a history of traumatic or inhaled exposure to soil (Shields & Castillo, 2002). Our patient possessed some risk factors, such as non-insulin-dependent diabetes, myelodysplastic syndrome, leukopenia, hyperglycaemia and occupational exposure. It is postulated that the inhalation of spores from soil may have been the infection source; he had a negative history of skin trauma and a normal chest radiograph.

To date, *C. bantiana*-induced CNS infections have been not reported in China, although many cases have been documented abroad. This could be related to mycological examination being applied only rarely in primary hospitals and the lack of knowledge of deep mycosis in clinicians in our country. CNS infections caused by *C. bantiana* can be present with brain abscess, and occasionally, meningitis, encephalitis, myelitis, arachnoiditis and necrotizing granuloma (Emmens *et al.*, 1996; Shields & Castillo, 2002; Revankar *et al.*, 2004; Deb *et al.*, 2005). The cerebral abscess can be single or multiple, characterized by headache, hemiparesis and focal deficits (seizure, cranial nerve palsy etc.) (Levin *et al.*, 2004; Revankar *et al.*, 2004; Garzoni *et al.*, 2008). Compared with the bacterial brain abscess, fever, nausea and vomiting were relatively uncommon in CNS phaeohyphomycosis (Revankar *et al.*, 2004; Garzoni *et al.*, 2008; Hakan, 2008). Histopathological and microbiological examinations are the diagnostic gold standard since fungal brain abscess cannot be differentiated from bacterial cerebral abscess, primary CNS tumour and cerebral metastasis by CT or magnetic resonance imaging (Garzoni *et al.*, 2008). Our patient presented with seizure, hemiparesis and occasional vomiting, but without fever, dizziness, headache and cranial nerve palsy. Therefore, mycological examination should be performed for the apyretic patient with cerebral abscess.

Combined antifungal chemotherapy, surgical debridement and careful immunological interventions have been strongly recommended for treating cerebral phaeohyphomycosis (Li & de Hoog, 2009). However, a standard therapy for cerebral *C. bantiana* infection has been unavailable to date, with a mortality rate of 70 % (Revankar *et al.*, 2004). Combination of different antifungals and complete resection of the abscess may improve the survival rate, and encapsulated lesions had a better prognosis compared to poorly encapsulated ones (Delfino *et al.*, 2006). *In vitro* susceptibility testing showed generally that *C. bantiana* is sensitive to itraconazole and voriconazole, and sensitive or resistant to amphotericin B and flucytosine, but resistant to fluconazole (Levin *et al.*, 2004; Lyons *et al.*, 2005; Delfino *et al.*, 2006; Garzoni *et al.*, 2008; Lakshmi *et al.*, 2008). Interestingly, two cases have

been treated successfully by fluconazole (Sood *et al.*, 2000; Delfino *et al.*, 2006). The treatment failure of the patient in our case could be related to immunosuppression, delayed diagnosis and unresponsive administration of a single antifungal. Therefore, this disorder should be treated with a combination of antifungal agents, immune enhancement and surgery.

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