Ramichloridium mackenziei brain abscess: report of two cases and review of the literature*

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We report two cases of brain abscesses caused by Ramichloridium mackenziei, a neurotropic dematiaceous fungus that seems to be geographically restricted to the Middle East. One of the patients had chronic myelomonocytic leukemia but did not receive any chemotherapeutic agents. The other patient was a normal host. Both cases had a fatal outcome despite aggressive antifungal therapy and surgical intervention. Herein, we review all previously described cases in the literature, and discuss the epidemiology, mycology and histopathology of this life-threatening organism.

Keywords brain abscess, dematiaceous fungi, Ramichloridium mackenziei, Saudi Arabia

Introduction

Systemic phaeohyphomycosis is a multisystemic disease caused by internal dissemination of a dematiaceous fungus. The portal of entry is usually the lung. However, in most cases the respiratory infection is asymptomatic [1]. Moreover, most patients first come to medical attention because of neurological problems. The list of dematiaceous fungi causing brain abscesses continues to grow. The most commonly reported fungus is Cladosphialophora bantiana, previously known as Xylohypha bantiana, Cladosporium bantianum and C. trichoides [2–5]. In addition, many other dematiaceous fungi including Ramichloridium mackenziei [6–10] have been described as causing brain abscesses. We report two Saudi Arabian patients with brain abscesses caused by R. mackenziei. We discuss the epidemiology, treatment and outcome of this aggressive invasive organism, and review the literature related to previously reported cases.

Case reports

Case 1

A 71-year-old Saudi male was diagnosed in January 1998 with chronic myelomonocytic leukemia. Two months later, he had a left inflamed nasal pterygium encroaching upon the cornea. He was treated with prednisolone ophthalmic solution and erythromycin ointment. Later, he developed a corneal ulcer. A culture taken late March 1998 from the cornea grew a dematiaceous fungus (Alternaria). Two weeks later, he was admitted with dizziness and an episode of loss of consciousness. Physical examination was unremarkable. Cardiac evaluation was unrevealing. The dizziness subsided and the patient was discharged home. Fifteen days later, the patient complained of left ankle pain and received intramuscular (IM) adrenocorticotropic hormone (ACTH) and oral colchicine for suspected gout. Four days later, he presented with a carbuncle in the left thigh, at the site of the IM injection. The abscess was incised and amoxicillin/clavulanate was prescribed. Cultures of the purulent material were negative. Three weeks later, he presented complaining of weakness on the left side and a slurred speech. On physical examination he was noted to have left-sided paralysis, with hyperreflexia, and an extensor plantar reflex. Contrast-enhanced computed...
tomography (CT) of the head showed a large lesion in the right parietal lobe with a marked mass effect (Fig. 1). Chest X-ray was normal. The patient underwent craniotomy. There were multiloculated thick walled cavities containing purulent material, which was evacuated. A frozen section performed on the brain tissue showed chronic granulomatous inflammation with septate hyphal elements. He was immediately started on Decadron, mannitol and amphotericin B that was increased rapidly to 50 mg day$^{-1}$. Oral itraconazole was added at 800 mg day$^{-1}$. The postoperative course was complicated by pulmonary embolism. On the tenth postoperative day, he sustained a cardiac arrest and expired.

Case 2

The patient was a 42-year-old Saudi male with a history of asthmatic bronchitis. On March 17, 1997 he presented complaining of progressive left thumb and index finger weakness that suddenly became worse two days before admission. He also had occasional headaches and drowsiness. Neurological examination revealed absent motor strength of the left thumb and index fingers, as well as left upper proximal muscle weakness. Complete blood count (CBC) was normal. Chest X-ray was unremarkable. A CT scan of the brain revealed a ring enhancing lesion in the right frontal lobe (Fig. 2). Craniotomy was performed and yellowish-brownish fluid was aspirated. No tissue was obtained. Cytological examination as well as Gram stain of the aspirated fluid showed numerous septate, pigmented hyphae. Bacterial cultures were negative. The patient received 12 days of 30 mg of amphotericin B that was later switched to oral fluconazole at 400 mg day$^{-1}$. Repeat CT scan of the brain revealed progressive cerebritis in the right parietal area with gyral enhancement and increased ring-like daughter abscess with worsening shift across the midline. The patient continued to deteriorate and had massive brain edema, which failed to respond to mannitol and Decadron. Amphotericin B was restarted. The area of frontal cerebritis was re-aspirated and continued to show fungal hyphae on Gram stain with no bacteria detected. Itraconazole at 200 mg per nasogastric tube was added. One day later, he lost his brainstem reflexes, and sustained a fatal cardiorespiratory arrest.

Histopathology

Several fragments of brain tissue were submitted from the first patient. They consisted of rubbery soft tan tissue, some admixed with blood, totaling 8 cm in aggregate diameter. There was heavy infiltration of the brain tissue by numerous lymphocytes, plasma cells and histiocytes. In addition, several well-formed granulomas composed of epithelioid histiocytes with many multinucleated giant cells were seen. The centers of these granulomas showed the presence of neutrophils. Several portions of septate hyphae were seen within these granulomas (Fig. 3). A few were irregular in shape as demonstrated by Gomori methenamine silver stain (Fig. 4). Some of these fungal elements were light yellowish brown in color. The presence of melanin was confirmed by Masson-Fontana stain. Other sections showed necrosis associated with heavy neutrophilic infiltrate (abscess formation) rimmed by a granulomatous inflammation. Numerous fungal hyphae were present within the purulent exudate.
Mycology

Brain tissue from the first patient and the purulent aspirate from the frontal lobe of the second patient were submitted for fungal culture. Specimens were inoculated onto Sabouraud peptone-glucose agar and mycophilic agar containing penicillin (100 U ml$^{-1}$) and gentamicin (100 μg ml$^{-1}$). Cultures were incubated at 37 and 28 °C. After 6 days, black, shiny, moist colonies were visible on both media. The reverse was black. Microscopic examination revealed melanized conidia. The isolates from both patients were referred to Mayo Medical Laboratories for identification.

Organisms were subcultured onto Sabouraud peptone-glucose agar. Colonies were black on both obverse and reverse. Microscopically, septate melanized hyphae and poorly differentiated conidiophores were present. Pale brown oval conidia were produced sympodially with an obvious dark hilum which protruded slightly. Conidia were attached to a sympodially proliferated axis (rachis); several were produced on each conidiophore (Fig. 5). Cultures grew at 42, 37 and 25 °C but there was better growth at 37 °C than at 25 and 42 °C.

Discussion

Many dematiaceous fungi, usually soil saprobes, can cause a wide spectrum of clinical manifestations including mycetoma, localized chromoblastomycosis and corneal ulcers, as well as systemic phaeohyphomycosis with sinusitis, pneumonia, and brain abscess [11,12]. In general, these fungi are of low virulence. However, after introduction into the dermis of normal hosts, some dematiaceous fungi can persist for a long time as agents of subcutaneous infection, without dissemination to other organs. Dermal infections in the normal host usually occur following soil contamination of preexisting wounds or with the introduction of foreign bodies such as wood splinters [13]. Immunocompromised patients, particularly solid organ transplant recipients, seem in general to be at a higher risk for subcutaneous as well as systemic infections [14,15]. However, cerebral phaeohyphomycosis has been reported in numerous immunocompetent patients. In a review of infections due to C. bantiana, 26 out 30 culture-documented cases involved the brain. Twenty of these 26 cases were immunocompetent with no apparent predisposing factors [3].

Some dematiaceous fungi have a predilection towards invasion of lung and brain tissue [6]. In these cases, the route of acquisition of these fungi is not certain, but the respiratory route is the likely portal of entry [8]. The location and the multiplicity of the brain lesions suggest a hematogenous spread from a distant focus. Dematiaceous fungi incriminated in brain abscesses are distributed worldwide and include C. bantiana [2–5], Exophiala dermatitidis [16,17], Chaetomium atrobrunneum [18], Bipolaris spicifera [19], B. hawaiensis [20], Rhinocladiella amagasakiensis [20], and Ramichloridium mackenziei.

Fig. 3  Brain tissue stained with Periodic acid Schiff stain demonstrating a granuloma with fungal hyphae present (magnification × 80).

Fig. 4  Brain tissue stained with Gomori methenamine silver stain featuring many fungal hyphae (magnification × 160).

Fig. 5  Ramichloridium mackenziei conidia attached to sympodially proliferated axis in vitro. (Polyvinyl alcohol-cotton blue preparation, magnification × 240).
diella atrovirens [21], Fonsecaea pedrosoi [22], Curvularia species [23], Ochroconis gallopavum [24], Scopulariopsis brumptii [25] and R. mackenziei [6–10].

R. mackenziei, the etiological agent in the present cases, is a neurotropic dematiaceous organism that is known to cause brain abscesses. Ten cases have previously been reported in the literature [6–10] (Table 1). Cerebral phaeohyphomycosis caused by R. mackenziei was first described in immunocompetent patients. Extensive immunological studies were done on three previously described patients. Serum immunoglobulin levels, complement hemolytic activity, and relative ratios of B-lymphocytes, T-helper lymphocytes and T-suppressor lymphocytes failed to show any abnormalities [8].

R. mackenziei seems to be geographically restricted to the Middle East, as all the cases described have been patients who have resided in that part of the world. In 1988, Naim-ur-Rahman et al. [8] were the first to report cases of brain abscesses caused by an organism they identified as R. obovoideum. These isolates were later identified as R. mackenziei [9]. They described three patients from Saudi Arabia. Two patients had a fatal outcome despite aggressive surgical drainage and antifungal chemotherapy. The third was discharged against medical advice and was lost to follow up.

A review published in 1993 of the recorded cases of brain abscess caused by the newly described R. mackenziei included five additional patients diagnosed over a three-year period [9]. Details of the patients are in Table 1. Prior to the new species description, attempts at identifying the etiological agent had been unsuccessful despite work done at Riyadh, Saudi Arabia, The Commonwealth Mycological Institute, Kew, Surrey, UK, and the Centers for Disease Control and Prevention, Atlanta, GA, USA [8]. Two of the isolates were initially misidentified as F. pedrosoi and as Cladosporium sp. One of the isolates was referred to Dr M. McGinnis’s laboratory in North Carolina, USA, and was identified as R. obovoideum. Ultimately, all these isolates were confirmed as R. mackenziei at the Mycology Laboratory in Bristol, UK [9].

R. mackenziei grows as black woolly domed colonies with a slow growth. Microscopically it produces few brown conidia [6] as described above. It shows variable growth in the presence of cycloheximide. It is distinguished in vitro from R. obovoideum by two characteristics: conidiophores that are not strongly differentiated from the vegetative hyphae and the lack of a yellow pigment that characteristically forms in R. obovoideum isolates.

Table 1  Cases of cerebral phaeohyphomycosis due to R. (obovoideum) mackenziei

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Country of residence</th>
<th>Underlying disease</th>
<th>Number of abscesses</th>
<th>Treatment</th>
<th>Outcome</th>
<th>[Ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>F</td>
<td>Saudi Arabia</td>
<td>None</td>
<td>Multiple</td>
<td>AMB, 5FC, KETO</td>
<td>Death</td>
<td>[8]</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>M</td>
<td>Saudi Arabia</td>
<td>None</td>
<td>Single</td>
<td>AMB</td>
<td>Death</td>
<td>[8]</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>Saudi Arabia</td>
<td>Bowel Surgery</td>
<td>Multiple (3)</td>
<td>AMB, 5FC</td>
<td>DAMA</td>
<td>[8]</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>F</td>
<td>Israel</td>
<td>Surgery</td>
<td>Single</td>
<td>NAD</td>
<td>NAD</td>
<td>[9]</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>M</td>
<td>Qatar</td>
<td>Kidney transplant</td>
<td>Single</td>
<td>AMB</td>
<td>Death</td>
<td>[9]</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>F</td>
<td>Oman</td>
<td>Kidney transplant</td>
<td>Single</td>
<td>NAD</td>
<td>NAD</td>
<td>[9]</td>
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<tr>
<td>7</td>
<td>NAD</td>
<td>NAD</td>
<td>United Arab Emirates</td>
<td>NAD</td>
<td>Single</td>
<td>NAD</td>
<td>Death</td>
<td>[9]</td>
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<tr>
<td>8</td>
<td>75</td>
<td>F</td>
<td>Saudi Arabia</td>
<td>None</td>
<td>Multiple (2)</td>
<td>NAD</td>
<td>Death</td>
<td>[9]</td>
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<tr>
<td>10</td>
<td>58</td>
<td>F</td>
<td>Kuwait</td>
<td>CRF</td>
<td>Multiple</td>
<td>AMB, ITRA</td>
<td>Death</td>
<td>[10]</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>M</td>
<td>Saudi Arabia</td>
<td>CMML</td>
<td>Single</td>
<td>Surgery, AMB, ITRA</td>
<td>Death</td>
<td>Case 1</td>
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<tr>
<td>12</td>
<td>42</td>
<td>M</td>
<td>Saudi Arabia</td>
<td>None</td>
<td>Single</td>
<td>AMB, FLUC, ITRA</td>
<td>Death</td>
<td>Case 2</td>
</tr>
</tbody>
</table>

AMB, amphotericin B; 5FC, 5-fluorocytosine; KETO, ketoconazole; ITRA, itraconazole; FLUC, fluconazole; CRF, chronic renal failure; CMML, chronic myelomonocytic leukemia; DAMA, discharged against medical advice; NAD, no available data; M, male; F, female.
Until more data exist on this fungus, we recommend that these fungal isolates be referred to reference laboratories for accurate identification and antifungal susceptibility testing against the newer agents that are being developed.

More recently, two patients referred from Middle Eastern countries were treated in the USA for brain abscesses due to *R. mackenziei*. Sutton et al. [6] described an Indian patient with Hodgkin’s disease who developed a brain abscess due to *R. mackenziei*. He had resided in Saudi Arabia for many years. The patient initially seemed to respond to the aggressive antifungal therapy that was started after surgical drainage. Although he was placed on 400 mg of itraconazole daily, he expired after 7 months. Podnos et al. [10] reported a 58-year-old Kuwaiti woman with chronic renal failure who presented with a 3-day history of headache, blurry vision, dizziness and right-sided clumsiness. CT scan demonstrated multiple ring-enhancing cerebral lesions in the deep left parieto-occipital region. Needle biopsy yielded 10 ml of dark fluid, and stains demonstrated fungal hyphae. A fungal culture grew, and was identified as *R. obovoideum*. The patient was treated with a combination of amphotericin B and itraconazole; however, the lesions progressed and she died. Her course of illness and management is similar to our second case.

The antifungal susceptibility of *R. mackenziei* is not well known. Previously one isolate was tested by the National Committee for Clinical Laboratory Standards (NCCLS) reference method for broth dilution antifungal susceptibility testing of yeast [26] and was found to be susceptible to amphotericin B, itraconazole and flucytosine [6] with minimum inhibitory concentration (MICs) values of 0.5–1, < 0.015 and 8 µg ml⁻¹, respectively. The MIC of fluconazole was 16 µg ml⁻¹, a concentration that can only be achieved with higher doses. Therefore, itraconazole should not be considered as the treatment of choice of this fungal infection. The clinical outcome of patients with brain abscesses due to *R. mackenziei* has been dismal with no correlation with *in vitro* data [6,9]. Moreover, standardization of susceptibility testing for filamentous fungi is only commencing [27]. Recently, Johnson et al. [28] reported that the *in vitro* activity of the new antifungal agent under investigation, Syn-2869, was comparable to itraconazole against *Ramichloridium mackenziei*. The patient was treated with a combination of amphotericin B and itraconazole; however, the lesions progressed and she died. Her course of illness and management is similar to our second case.

The antimicrobial susceptibility of *R. mackenziei* is not well known. Previously one isolate was tested by the National Committee for Clinical Laboratory Standards (NCCLS) reference method for broth dilution antimicrobial susceptibility testing of yeast [26] and was found to be susceptible to amphotericin B, itraconazole and flucytosine [6] with minimum inhibitory concentration (MICs) values of 0.5–1, < 0.015 and 8 µg ml⁻¹, respectively. The MIC of fluconazole was 16 µg ml⁻¹, a concentration that can only be achieved with higher doses. Therefore, fluconazole should not be considered as the treatment of choice of this fungal infection. The clinical outcome of patients with brain abscesses due to *R. mackenziei* has been dismal with no correlation with *in vitro* data [6,9]. Moreover, standardization of susceptibility testing for filamentous fungi is only beginning [27]. Recently, Johnson et al. [28] reported that the *in vitro* activity of the new antifungal agent under investigation, Syn-2869, was comparable to itraconazole against *R. mackenziei*.

The two patients described in this report are both from the Eastern Province of Saudi Arabia, which is located by the Arabian Gulf and has a humid environment with temperatures reaching above 40 °C in the summer time. The previously reported cases were residents of Saudi Arabia, Qatar, United Arab Emirates, Kuwait and Israel. It is unclear why this fungus is apparently restricted to the Middle East region. Further studies into its biology and epidemiology are needed.

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**References**


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