Cerebral phaeohyphomycosis due to *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*): Case presentation and literature review

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**KEYWORDS**
Phaeohyphomycosis; *Rhinocladiella mackenziei*; *Ramichloridium mackenziei*

**Summary** *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*), a causative agent of cerebral phaeohyphomycosis, is extremely rare and it is geographically limited to the Middle East. The organism has a predilection to cause brain infections and results in a grave prognosis with a high mortality rate. The current patient was admitted to a long term care facility with chronic respiratory failure and dependence on a mechanical ventilator. She later developed left sided weakness and a CT-scan of the brain revealed multiple variable sized hypodense, well-defined lesions with ring enhancement. A stereotactic needle aspiration of the largest lesion showed fungal hyphae. The final culture grew *R. mackenziei*. The patient was initially started on liposomal amphotericin B, then voriconazole and caspofungin intravenously as posaconazole was not available. The patient failed to respond to antifungal therapy and finally she died 34 days after the start of the treatment. *R. mackenziei* is a highly virulent agent, and should be considered in the differential diagnosis of central nervous system disease in patients from the Middle East.

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**Introduction**

Cerebral phaeohyphomycosis is an infection caused by dematiaceous fungi especially in immunocompromized patients [1–3]. Of the dematiaceous fungi known to be neurotrophic include *Cladophialophora bantiana*, *Wangiella dermatitidis*.
Cerebral phaeohyphomycosis due to *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*) and *Chaetomium atrobrunneum* [4–7]. In addition, *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*) has been reported to be a causative agent of fatal cases of *R. mackenziei* infection [1–3]. *R. mackenziei* infection appears to occur predominantly in the Middle East and to target the brain exclusively [1–3]. However, it should be noted that *R. mackenziei* has not been recovered from any environmental source [3]. Recently, two cases were reported from areas outside of the Middle East, mainly from India and Afghanistan [8, 9].

In this report we describe an additional fatal case of *R. mackenziei* cerebral infection, and review the clinical characteristics, the treatment and outcome of this infection.

**Case presentation**

The patient, a 64 year old Saudi female, was admitted initially to a long term care facility with chronic respiratory failure and dependence on the mechanical ventilation. The patient was known to have chronic respiratory failure secondary to chronic obstructive pulmonary disease. She required hemodialysis multiple times due to diabetic nephropathy. She remained stable on mechanical ventilation for a few months. Four days prior to transfer to our hospital, she was noticed to be sleepy with left sided weakness. There was no history of fever, chills, nausea or vomiting. A computerized axial tomography (CAT) scan of the brain revealed multiple variable sized hypodense, well-defined right parieto-occipital lesions with ring enhancement. The lesions were surrounded by moderate vasogenic edema with compression of the adjacent left lateral ventricles (Fig. 1). The patient was transferred to our institution for further work up and management.

Past medical history was remarkable for type 2 diabetes mellitus, diabetic retinopathy and nephropathy. In addition, she had hyperlipidemia, hypertension, and congestive heart failure.

Physical examination revealed an elderly female with stable vital signs, a temperature of 36.5 °C, blood pressure of 122/75, heart rate of 80/min and an oxygen saturation of 99%. Chest examination revealed reduced breath sounds with expiratory wheezing. Examination of the abdomen and the heart were normal. There was Lower limb edema. Neurologically, she was awake however she did not follow verbal commands. She had minimal movement of the right limbs to stimulation with decreased tendon reflexes and no movement in the other limbs.

The magnetic resonance imaging (MRI) of the brain showed multiple variable sized heterogeneous hyperintense predominantly T2 lesions localized to the deep right posterior frontal and parieto-occipital lobes. The largest lesion measured 5.0 × 4.1 × 4.3 cm’s (Fig. 2). There was massive bilateral paranchymal vasogenic edema but involved the right hemisphere more than left hemisphere.

The patient underwent a stereotactic needle aspiration of the largest lesion in the right parieto-occipital area. The gram stain showed fungal hyphae. Patient was initially started on liposomal amphotericin B, however the antifungal medication was changed to voriconazole and caspofungin intravenously as posaconazole was not available. A repeat CT of brain, 18 days after initiation of the treatment, revealed worsening massive vasogenic edema involving the right tempor-parietal lobe right thalamus, and crosses the posterior corpus callosum to the contralateral side. Due to the severity of the illness, the patient continued to deteriorate and she died 34 days after the start of the treatment.

**Mycological findings**

Smears of the aspirated brain abscess were stained with both Gram stain and hematoxylin and eosin stains. The smears revealed acute inflammatory exudate admixed with numerous neutrophils. In addition, many fungal septate hyphae were seen (Fig. 3). The aspirate was inoculated at 25 °C on slant tubes of Sabouraud’s glucose agar and mycological agar media. After 22 days, fluffy brown to dark olive green colonies with raised edges at the periphery appeared. The isolated organism was sent to the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio, Texas (USA). The final result was available about 4-week after the death of the patient. The organism was identified as *R. mackenziei*. Unfortunately, no antifungal susceptibility testing was done.

**Discussion**

Infection by *R. mackenziei* targets the cerebrum exclusively. A total of 27 cases were reported previously (Table 1) and here we report an additional case. *R. mackenziei* is thought to be restricted to the Middle East [17]. It is interesting to note that out of the reported cases, 13 (46%) cases were from Saudi Arabia. However, *R. mackenziei*...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Age (years)/sex</th>
<th>Underlying condition</th>
<th>No. of abscesses</th>
<th>Surgical drainage</th>
<th>Antifungal therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[10,11]</td>
<td>Saudi Arabia</td>
<td>55/F</td>
<td>None</td>
<td>Multiple</td>
<td>Yes</td>
<td>AmB, 5-FC, KTZ</td>
<td>Died after 6 months</td>
</tr>
<tr>
<td>[10,11]</td>
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<td>80/M</td>
<td>None</td>
<td>Solitary</td>
<td>Yes</td>
<td>AmB, 5-FC, KTZ</td>
<td>Died after 2 months</td>
</tr>
<tr>
<td>[10]</td>
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<td>70/M</td>
<td>Bowel surgery</td>
<td>Multiple</td>
<td>Yes</td>
<td>AmB, 5-FC</td>
<td>NA</td>
</tr>
<tr>
<td>[10]</td>
<td>Israel</td>
<td>60/F</td>
<td>NA</td>
<td>Solitary</td>
<td>Aspirate</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>[10]</td>
<td>Qatar</td>
<td>55/M</td>
<td>Kidney transplant</td>
<td>Solitary</td>
<td>Aspirate</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
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<td>Aspirate</td>
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<td>NA</td>
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<td>[10]</td>
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<td>NA</td>
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<td>Aspirate</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>[10]</td>
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<td>75/M</td>
<td>None</td>
<td>Multiple</td>
<td>Aspirate</td>
<td>NA</td>
<td>Died</td>
</tr>
<tr>
<td>[10]</td>
<td>Saudi Arabia</td>
<td>60/M</td>
<td>None</td>
<td>Multiple</td>
<td>Yes</td>
<td>AmB, 5-FC, KTZ</td>
<td>Died after 8 weeks</td>
</tr>
<tr>
<td>[10]</td>
<td>Saudi Arabia</td>
<td>36/M</td>
<td>Hodgkin’s disease in remission</td>
<td>Solitary</td>
<td>Yes</td>
<td>ITZ</td>
<td>Died after 8 months</td>
</tr>
<tr>
<td>[14]</td>
<td>Saudi Arabia</td>
<td>71/M</td>
<td>Chronic myelogenous leukemia</td>
<td>Solitary</td>
<td>Yes</td>
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<td>Died after 10 days</td>
</tr>
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<td>[14]</td>
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<td>42/M</td>
<td>None</td>
<td>Solitary</td>
<td>Yes</td>
<td>AmB, ITZ</td>
<td>Died after 2 weeks</td>
</tr>
<tr>
<td>[15]</td>
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<td>67/F</td>
<td>Diabetes mellitus</td>
<td>Solitary</td>
<td>Aspirate</td>
<td>AmB</td>
<td>Died after 10 days</td>
</tr>
<tr>
<td>[16]</td>
<td>Kuwait</td>
<td>56/M</td>
<td>Chronic liver disease</td>
<td>Solitary</td>
<td>Yes</td>
<td>AmB</td>
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<td>[3]</td>
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<td>62/M</td>
<td>Renal transplant</td>
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<td>Aspirate</td>
<td>LAmb, ITZ, 5-FC then Posa</td>
<td>Cured</td>
</tr>
<tr>
<td>[1]</td>
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<td>66/F</td>
<td>Diabetes mellitus</td>
<td>Multiple</td>
<td>Aspirate</td>
<td>LAmb, VOR</td>
<td>Died after 5 weeks</td>
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<tr>
<td>[17]</td>
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<td>59/F</td>
<td>Breast cancer on chemotherapy</td>
<td>Multiple</td>
<td>Aspirate</td>
<td>LAmb, VOR</td>
<td>Died after 64 days</td>
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<td>[8]</td>
<td>India</td>
<td>50/M</td>
<td>Diabetes mellitus</td>
<td>Solitary</td>
<td>Yes</td>
<td>AmB</td>
<td>Died after 2 weeks</td>
</tr>
<tr>
<td>[9]</td>
<td>Afghanistan</td>
<td>80/F</td>
<td>None</td>
<td>Multiple</td>
<td>Aspirate</td>
<td>VOR, POSA</td>
<td>Died after 7 months</td>
</tr>
<tr>
<td>[18]</td>
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<td>45/M</td>
<td>Diabetes Mellitus</td>
<td>Multiple</td>
<td>Aspirate</td>
<td>AmB, ITZ</td>
<td>Died at 1 month</td>
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<td>30/M</td>
<td>Head Injury</td>
<td>Solitary</td>
<td>Yes</td>
<td>AmB, ITZ</td>
<td>Alive at 10 months</td>
</tr>
<tr>
<td>[18]</td>
<td>Pakistan</td>
<td>45/M</td>
<td>None</td>
<td>not known</td>
<td>Yes</td>
<td>AmB, ITZ</td>
<td>NA</td>
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<td>20/F</td>
<td>Trauma</td>
<td>Solitary</td>
<td>Aspirate</td>
<td>AmB, ITZ</td>
<td>Alive at 12 months</td>
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<tr>
<td>[18]</td>
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<td>53/M</td>
<td>Liver transplant</td>
<td>Solitary</td>
<td>Yes</td>
<td>AmB</td>
<td>Died at 2 months</td>
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<tr>
<td>[18]</td>
<td>Pakistan</td>
<td>75/M</td>
<td>History of tuberculosis</td>
<td>Solitary</td>
<td>Yes</td>
<td>ITZ</td>
<td>Alive at 2 months</td>
</tr>
<tr>
<td>Current</td>
<td>Saudi Arabia</td>
<td>64/F</td>
<td>Diabetes mellitus</td>
<td>Multiple</td>
<td>Aspirate</td>
<td>LAmb, then VOR + caspo</td>
<td>Died after 34 days</td>
</tr>
</tbody>
</table>

F, female; M, male; NA, not available.

Antifungal therapy: AmB, amphotericin B; 5FC, 5-flourocytocine; ITZ, itraconazole; FLC, fluconazole; VRC, voriconazole; KTZ, ketoconazole; POS, posaconazole; ANIDO, anidulafungin; MICA, micafungin; CASPO, caspofungin.
Cerebral phaeohyphomycosis due to *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*)

Figure 1  A computerized axial tomography (CAT) scan of the brain showing multiple variable sized hypodence, well-defined right parieto-occipital lesions with ring enhancement and moderate vasogenic edema.

has never been isolated from the environment in the country [3]. Thus, the natural niche of this organism remains unknown. Recently patients with *R. mackenziei* brain abscesses were reported from India [8] and Afghanistan [9]. The Indian strain (CBS 125089) originated from a humid subtropical climate and infected a patient who claimed he had never traveled outside India [8]. The other patient also did not have any travel history to the Middle East [9]. Additionally, a total of six new cases were reported from Pakistan [18]. Thus, the cases do not seem to be restricted to the Middle East as it was thought previously.

Most of the patients (60.7%) with *R. mackenziei* brain abscess presented with solitary brain abscesses and the remaining had multiple lesions. However, the current patient had multiple lesions similar to the remaining (39.3%) of the cases.
Surgical drainage was done in 53% of patients, and the remaining patients had aspiration only (Table 1). The current patient did not have surgical resection since she had multiple brain lesions. However, surgical resection does not seem to have major impact on survival. Of the reported cases, mortality rate was comparable in those who underwent surgical resection (84.5%) and those who did not have surgical resection (82%). The outcome may be difficult to ascertain since the patients received different anti-fungal therapies. The most commonly used antifungal agent was amphotericin B (71.4%) alone or in combination (Table 1). In a murine model of *R. mackenziei* cerebral phaeohyphomycosis, posaconazole was superior to amphotericin B and itraconazole and reduced the brain fungal burden [19]. We previously used posaconazole in the treatment of *R. mackenziei* brain abscess and showed a prolonged survival of 4 years [3]. However, posaconazole was recently tried in one patient but the patient died within 7 months of therapy [9]. Unfortunately, there was no antifungal sensitivity testing done for the current isolate. However, a summary of the available data for in vitro antifungal susceptibility testing for eight strains of *R. mackenziei* is shown in Table 2. Amphotericin B susceptibility seems to be strain-dependent and the MICs for fluconazole and 5-flucytosine were high [17]. On the other hand, the MIC values against itraconazole, voriconazole, posaconazole and isavuconazole is difficult to interpret [17]. It seems also that there is no correlation between in vitro results and in vivo response in the case of the azoles [17]. This is thought to be due to pharmacokinetics of the drug, combined with host factors. An open label clinical trial of the efficacy of posaconazole in the treatment of patients with CNS fungal infections showed that posaconazole was successful in 48% (14 of 29) of the patients with cryptococcal infection and in 50% (5 of 10) of patients infected with other fungal pathogens [20]. However, posaconazole is not currently approved for this indication [21]. In addition, the efficacy of the different antifungal agents in the clinical practice against dematiaceous fungi in general and against *R. mackenziei* is not well documented. The mortality rate of cerebral phaeohyphomycosis due to *R. mackenziei* is associated with a high mortality rate of 83.3% of all cases with documented outcome. However, some of the cases were followed up for a short duration of less than a year [18]. The patient in the current report died within 1 month of the diagnosis. This finding is slightly less than the average survival rate of about 2 months after the diagnosis (Table 1).
Cerebral phaeohyphomycosis due to \textit{Rhinocladiella mackenziei} (formerly \textit{Ramichloridium mackenziei})

In conclusion, \textit{R. mackenziei} infection of the central nervous system is a challenging disease with a high mortality rate. Successful therapy of this serious infection does not seem to be related to surgical intervention and the available therapy. The optimal antifungal agent is not yet identified. Patients with this disease may also need prolonged suppressive antifungal therapy.

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Conflict of interest statement

\textbf{Funding:} No funding sources.  
\textbf{Competing interests:} None declared.  
\textbf{Ethical approval:} Not required.

References


\begin{table}[h]
\centering
\caption{Antifungal susceptibility testing results (MIC $\mu$g/ml) for \textit{Rhinocladiella mackenziei} in different studies.}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|c|}
\hline
Reference & AmB & 5-FC & ITZ & FLC & VOR & KTZ & POS & ANIDO & MICA & CASPO & Isavuconazole \\
\hline
[1] & 0.3 & 4 & <0.015 & <0.015 & <0.015 & 0.015 & & & & & \\
[3] & 1 & 16 & <0.015 & 0.015 & & & & & & & \\
[8] & 16 & 0.063 & 32 & 0.5 & 0.031 & 4 & 8 & 0.5 & & & \\
[12] & 1 & 8 & <0.015 & 16 & & & & & & & \\
[16] & >32 & 16 & 0.125 & 32 & 0.5 & 0.25 & & & & & \\
[17] & 16 & <0.03 & <0.03 & & & & <0.03 & 4 & 1 & 1 & \\
[19] & >16 & <0.015 & 32 & & & 0.25 & & & & & \\
[19] & 1 & <0.015 & 16 & & & 0.03 & & & & & \\
\hline
\end{tabular}
\end{table}

