

## CEREBRAL PHAEOPHYCOMYCOSIS CAUSED BY *RAMICHLORIDIUM MACKENZIEI* IN THE EASTERN PROVINCE OF SAUDI ARABIA

Tahir Q. Kashgari, DMRD; Hani Al-Miniawi, MD;  
Maher K. Moawad Hanna, MSc, PhD

A brain abscess is a localized collection of pus within the brain parenchyma<sup>1</sup> or meninges. A wide range of microorganisms have been identified as causative agents, depending on the source of infection and predisposing conditions.<sup>2-5</sup> A few published data are available on the microbiology of cerebral abscesses from developing countries.<sup>6-8</sup> Human brain abscesses due to fungi are mostly seen in immunocompromised patients with opportunistic infections. They have also been seen in patients on cytotoxic drugs, long-term corticosteroid treatment, and those with diabetes mellitus.<sup>9</sup> These abscesses have been caused by various species such as *Aspergillus*, *Candida*, *Zygomycetes*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Pseudallescheria boydii*. However, basidiomycete *Schizophyllum commune* has also been reported as an emerging pathogen which was found involving the lungs of a 58-year-old patient, with subsequent dissemination to the brain.<sup>10</sup>

Phaeoerythromycosis is a term initially proposed by Ajello and Georg<sup>11</sup> in 1974 for fungal infection characterized by dematiaceous (because of the dark pigment, dihydroxy-naphthalene melanin, present in the cell wall) septated mycelial elements in tissues. The more general term, "cerebral phaeoerythromycosis," is applicable to all brain infections caused by dematiaceous fungi. These organisms are being increasingly recognized as opportunistic pathogens that can cause serious disease in immunocompromised patients.<sup>12</sup> The most frequently reported pathogen of this group is *Xylohypha bantiana* (previously known as *Cladosporium trichoides* or *C. bantiana*).<sup>13</sup> The rarer pathogens are *Bipolaris hawaiiensis*, *B. spicifera*, *Chaetomium globosum*, *Scopulariopsis brumptii*, *Dactylaria gallopava*, and *Dreschlera spicifera*.

From Riyadh, Saudi Arabia, Jinkins et al.<sup>14</sup> reported five cases with differing forms and severity of cranial aspergillosis. In 1989, Ur-Rahman et al.,<sup>15</sup> also from Riyadh, reported a multiple phaeoerythromycotic brain

Address reprint requests and correspondence to Dr. Kashgari: P.O. Box 12351, Dammam 31473, Saudi Arabia.

Accepted for publication 5 June 2000. Received 2 November 1999.

abscess caused by *Cladosporium* spp. in a Saudi female, after the culture had been identified as *Ramichloridium obovoideum* by the Clinical Microbiology Laboratories in North Carolina, U.S.A. In 1988, Ur-Rahman et al. again reported three cases caused by *R. obovoideum*.<sup>16</sup> Al-Hedaithy et al. from the same hospital as Ur-Rahman (King Khalid University Hospital) independently identified the causal fungus in the three cases to be *Fonsecaea pedrosoi*.<sup>17</sup> These three isolates, in addition to another unidentified isolate in 1991 have undergone taxonomic evaluation by Campbell and Al-Hedaithy, and were reclassified as *Ramichloridium mackenziei* spp. in 1993.<sup>18</sup> This fungus has also been considered by these authors in the same publication as the etiologic agent responsible for four previous cases in other Middle Eastern countries. To our knowledge, only these eight cases of brain abscesses due to *R. mackenziei* have been reported since 1993. In 1994, Jamjoom et al. reported three cases of brain abscesses caused by *Actinomyces israelii*, which were successfully treated by burr-hole aspiration and a short course of antibiotics (3-4 weeks).<sup>19</sup> In 1995, Jamjoom et al.,<sup>20</sup> in their retrospective study on intracranial mycotic infections in neurosurgical practice over an eight-year period, again reported mycotic intracranial lesions in eight out of the 17 cases in the study. *Actinomyces israelii* was responsible for the three cases (previously reported in 1994) and *Nocardia asteroides* for one, in addition to the four cases caused by *R. mackenziei*. In 1996, Ur-Rahman et al.<sup>21</sup> reported nine cases of cranial and intracranial aspergillosis of sinonasal origin.

In 1989, Basit et al.<sup>6</sup> reported 21 pyogenic brain abscesses out of 179 cases examined between 1976 and 1984 at the Dammam Central Hospital in the Eastern Province of Saudi Arabia. In 1990, Ibrahim et al.<sup>22</sup> reported 26 cases of brain abscess between 1982 and 1988. None of the examined cases reported by these authors in their publications were of mycotic origin.

CT scan is very helpful in delineating the location and character of fungal brain lesions. Contrast enhancement on CT scan or MRI depends on vascularity and disruption of the brain barrier.<sup>23</sup> We recently treated unsuccessfully two serious cases of brain abscess due to *R. mackenziei* in the

From the Departments of Radiology and Neurosurgery (Drs. Kashgari and Al-Miniawi), Dammam Central Hospital, and the Department of Mycology (Dr. Hanna), Regional Laboratory and Blood Bank, Dammam, Saudi Arabia.

Eastern Province of Saudi Arabia. This is a report of these two cases and a discussion of the diagnostic CT scan implication of pyogenic brain abscesses.



FIGURE 1. Branched septate hyphae of *Ramichloridium mackenziei* in gram-stained smears of aspirated pus from brain abscess in case 1 (370x).

#### Case 1

A 67-year-old Saudi female, a known case of psychiatric illness, diabetes mellitus, hypertension and dizziness, convulsions and headache, attended the Neurosurgical Department. A brain CT scan with contrast revealed a ring-enhancing lesion with a central ring-like high attenuation in the left parietal region. The patient underwent stereotactic aspiration of the lesion, which turned out to be an abscess. Initial culture sensitivity was reported by the bacteriology laboratory to have *Staphylococcus epidermidis*. The patient was given proper antibiotics according to the sensitivity report (cloxacillin and flagyl). Two weeks later, a repeated CT scan revealed no change in the abscess size, therefore, re-aspiration was done. The purulent material was removed and sent to both bacteriology and mycology laboratories. Immediate microscopic examination of gram-stained smears was carried out which demonstrated fungus elements (Figure 1), as did cultures of the pus (Figure 2). The isolated pathogen was identified as a dematiaceous fungus, and proven later to be *R. mackenziei* (U.K. National Collection of Pathogenic Fungi as NCPF 7123, Public Health Laboratory, Mycology Reference Laboratory, Bristol, U.K.) Therapy with intravenous amphotericin B was started. A repeated CT scan after eight days showed improvement, but all of a sudden, the patient complained of fever and urinary tract infection and died two days later.

#### Case 2

A 65-year-old Saudi female, who was being treated for myelofibrosis and Hodgkin's lymphoma (nodular sclerosis) attended the Neurosurgical Department suffering from fatigability, palpitations and fever for a duration of three

days. Pre- and post-contrast brain CT scans showed a well-defined low-attenuated ring-enhancing lesion with a central high-attenuated ring-like appearance in the right parietal region (Figure 3). This was followed by a CT scan to locate the abscess, and pus was aspirated by emergency burr-hole operation. The pus was sent to both bacteriology and myco-



FIGURE 2. *Ramichloridium mackenziei*. Microscopic morphology, Case 1 (acid fuchsin, 400x).

logy departments. Immediate microscopic examination of the gram-stained smears was carried out, which demonstrated mainly fungus elements. Cultures were positive for *R. mackenziei* and *Pseudomonas* spp. (bacteria as secondary infection) (Figure 4). The patient received both amphotericin B and gentamicin (i.v.), however, her condition progressively worsened despite surgical drainage and the intravenous antifungal and antibiotic therapy. The patient died approximately three weeks after her initial CT scan.

### Discussion

Brain abscess is a deadly complication of immunosuppression, particularly in patients with diabetes and/or Hodgkin's lymphoma. Although the morbidity and mortality associated with brain abscesses have been decreasing in the past 20 years, problems persist in the areas of early diagnosis, identification of responsible pathogens and effective medical and surgical treatment. In 1993, Campbell and Al-Hedaithy<sup>18</sup> published the first report of brain abscesses caused by an unusual phaeohyphomycete classified as *R. mackenziei* spp., which were isolated from four cases of brain abscesses from the Central Province of Saudi Arabia. This fungus has a limited geographic distribution, as it has been considered the cause of these four cases in Saudi Arabia and another four cases in other Middle Eastern countries (only one patient had travelled outside the Middle East during the course of illness.<sup>18</sup>) The two cases presented here are the

first proven infections of cerebral phaeohyphomycosis caused by *R. mackenziei* in the Eastern Province of Saudi Arabia. In addition, one of the two cases is due to this fungus mixed with *Pseudomonas* spp. (bacteria). Upon reviewing the literature, the overall incidence of *Pseudomonas* as the main causative organism has been found to be low.<sup>1,24,25</sup>

The typical CT scan picture of a cerebral abscess is that of a ring-like lesion with a low attenuation core.<sup>26,27</sup> The minimal ring enhancement was probably an effect of steroid

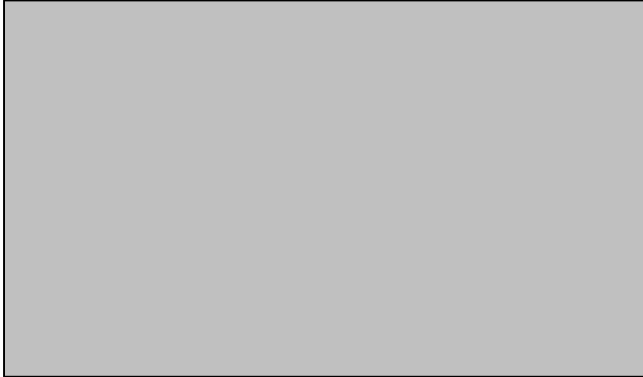


FIGURE 3. Post-contrast brain CT scan showing well-defined, rounded low-attenuated lesion with central ring-like high attenuation (Case 2).

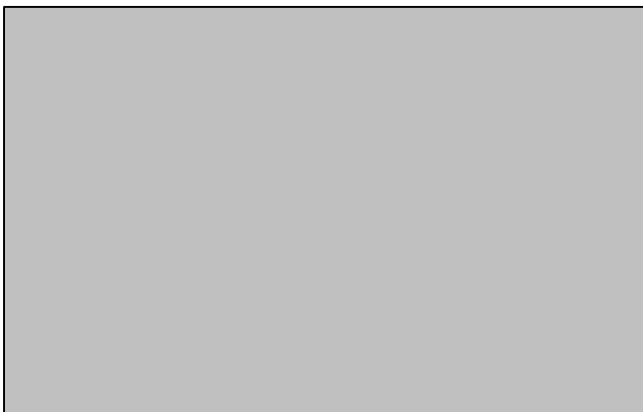


FIGURE 4. *Ramichloridium mackenziei* (Case 2). Subculture of the fungus at 3 weeks at 30°C.

treatment, which is known to suppress the peripheral enhancement of abscesses.<sup>26,28</sup> The high attenuation core of the lesion could have resulted from secondary hemorrhage.<sup>29</sup>

Hypodense lesions with peripheral ring enhancement in brain abscess have been reported in cerebral phaeohyphomycosis<sup>18</sup> and in neonatal brain abscess caused by *Morganella morganii* (bacteria).<sup>30</sup> In 1994, Hagnese et al.<sup>31</sup> in their report on fungal brain abscesses in 58 cases of different agents described typically multifocal hypodense non-enhancing lesions with mass effect in aspergillus infections (26 cases), while the majority of brain abscesses caused by *Candida* had normal scans.

Non-detailed ring-enhancement lesions in the brain have been described by some authors.<sup>20,33</sup> Non-contrast CT scan of brain abscess caused by *Candida albicans* showed hypodense area involving the head of the right caudate nucleus.<sup>34</sup> However, multiple high-density lesions of different sizes have been described in another case of cerebral candidiasis.<sup>23</sup> The CT scan in a case of brain abscess caused by *Blastomyces dermatitidis* demonstrated a left cerebral mass that was enhanced by contrast.<sup>35</sup> A TB brain abscess with non-detailed ring-enhancing lesions has been described in an AIDS patient,<sup>33</sup> yet in another publication, a CT scan showed a ring-enhancing low-attenuated lesion.<sup>36</sup> Toxoplasmosis brain abscess typically manifests on CT scan and MRI as nodular (small encephalitis) and/or ring-enhancing (large abscess) lesions within the brain parenchyma. *Cryptococcus* brain abscess in CT scan and MRI generally appears as discrete nodular or ring-enhancing masses.<sup>36</sup> Areas of abnormal enhancement have been described in a case of cerebral mucormycosis brain abscess.<sup>37</sup>

In MRI findings of brain abscesses, heterogeneous mass lesions, contrast-enhanced mass lesion, and multiloculated cystic lesion with marked brain edema adjacent to the lesion have been described by some authors.<sup>10,15,37,38</sup>

Of particular interest to the CT scan of our two cases of Hodgkin's lymphoma and the severely diabetic patients with brain abscesses was the presentation of a central ring-like high attenuation (most probably due to secondary hemorrhage), in addition to the classical, well-defined, ring-enhancing low-attenuated lesions. This could be related to the severity of the infecting organism (*R. mackenziei*).

### Acknowledgements

The authors gratefully acknowledge Dr. Campbell (Deputy Head, Mycology Reference Laboratory) and Dr. Johnson (Public Health Laboratory, Bristol, U.K.) for the identification of the isolated pathogen. We also express our sincere gratitude to the staff of the Radiology and Neurosurgery Departments (Dammam Central Hospital,

Eastern Province, Saudi Arabia) for their continuous interest in, and enthusiastic support for, our work.

### References

- Twomey CR. Brain abscess: an update. *J Neurosc Nurs* 1992;24:34-9.
- De Louvois J, Gortavai P, Hurley R. Bacteriology of abscesses of the central nervous system. Multicentre Prospective Study. *BMJ* 1977;2: 81-4.
- Grace A, Drake-Lee A. Role of anaerobes in cerebral abscesses of sinus origin. *BMJ* 1983;288:758-9.
- Richards J, Sisson PR, Hickman JE, Ingham HR. Microbiology, chemotherapy mortality of brain abscess in Newcastle-Upon-Tyne between 1979 and 1988. *Scand J Infect Dis* 1990;22:511-8.
- Schliamsner SE, Backman K, Norrby SR. Intracranial abscesses in adults: an analysis of 54 consecutive cases. *Scand J Infect Dis* 1988;20: 1-9.
- Basit AS, Ravi B, Banerji AK, Tandon PN. Multiple pyogenic brain abscesses: an analysis of 21 patients. *J Neurol Neurosurg Psychiatr* 1989;52:591-4.
- Jamjoom A. Childhood brain abscess in Saudi Arabia. *Ann Trop Paediatr* 1997;17:95-9.
- Puay YNG, Seow WT, Ong PL. Brain abscesses: review of 30 cases treated with surgery. *Aust N Z J Surg* 1995;65:664-6.
- Brid NS, Kulkarni AG, Kale MM, Shah PJ, Yadav SR. Ring-enhancing lesions on computed tomography. *Postgrad Med J* 1997;73: 355-6.
- Rihs JD, Padhye AA, Good CB. Brain abscess caused by *Schizophyllum commune*: an emerging *Basidiomycete* pathogen. *J Clin Microbiol* 1996;34:1628-32.
- Ajello L, Georg LK, Steigbigel, Wang JC. A case of phaeohyphomycosis caused by a new species of *Phialophora*. *Mycologia* 1974;66:490-8.
- Yoshimori RN, Moore RA, Itabashi HH, Fujikawa DG. Phaeohyphomycosis of the brain. Granulomatous encephalitis caused by *Drechslera spicifera*. *Am J Clin Pathol* 1982;77:363-70.
- Buxi TBS, Prakash K, Vohra R, Bhatia D. Imaging in phaeohyphomycosis of the brain: case report. *Neuroradiology* 1996;38:1399-41.
- Jenkins JR, Siqueira E, Al-Kawi MZ. Cranial manifestations of aspergillosis. *Neuroradiology* 1987;29:181-5.
- Ur-Rahman N, Mahgoub S, Abu-Aisha H, Laajam M, Yaquob B. Cerebral phaeohyphomycosis. *Bull Soc Pathol Exot Fil* 1987;80:320-8.
- Ur-Rahman N, Mahgoub ES, Chagla AH. Fatal brain abscesses caused by *Ramichloridium obovoideum*: report of three cases. *Acta Neurochir* 1988;93:92-5.
- Al-Hedaithy SA, Jamjoom ZAB, Saeed ES. Cerebral phaeohyphomycosis caused by *Fonsecaea pedrosoi* in Saudi Arabia. *Acta Pathol Microbiol Scand* 1988;96(Suppl 3):94-100.
- Campbell CK, Al-Hedaithy SS. Phaeohyphomycosis of the brain caused by *Ramichloridium mackenziei* spp. in Middle Eastern countries. *J Med Vet Mycol* 1993;31:325-32.
- Jamjoom AB, Jamjoom ZAB, Al-Hedaithy SS. Actinomycetic brain abscess successfully treated by burr-hole aspiration and short course antimicrobial therapy. *Br J Neurosurg* 1994;8:545-50.
- Jamjoom AB, Al-Hedaithy SSA, Jamjoom ZAB, Al-Hedaithy M, El-Watidy SF, et al. Intracranial mycotic infections in neurosurgical practice. *Acta Neurochir (Wien)* 1995;137:78-84.
- Ur-Rahman N, Jamjoom A, Al-Hedaithy SSA, Jamjoom ZAB, Al-Sohaibani MO, et al. Cranial and intracranial aspergillosis of sino-nasal origin. *Acta Neurochir (Wien)* 1996;138:944-50.
- Ibrahim AW, Al-Rajeh SM, Showdhary UM, Ammar A. Brain abscess in Saudi Arabia (review). *Neurosurg Rev* 1990;13:103-7.
- Johnson SC, Kazzi NJ. *Candida* brain abscess: a sonographic mimicker of intracranial hemorrhage. *J Ultrasound Med* 1993;4:237-39.
- Tiffany KK, Kline MW. Mixed flora brain abscess with *Pseudomonas paucimobilis* after a penetrating lawn dart injury. *Pediatr Infect Dis J* 1988;7:667-9.
- Gupta SK, Mohanty SM, Tandon S, Asthana S. Brain abscess: with special reference to infection by *Pseudomonas*. *Br J Neurosurg* 1990; 4:297-86.
- Whelan MA, Hilal SK. Computed tomography as a guide in the diagnosis and follow-up of brain abscesses. *Radiology* 1980;135:663-71.
- Britt RH, Enzymann DR. Clinical stages of human brain abscesses on serial CT scans after contrast infusion. *J Neurosurg* 1983;59:972-89.
- Quartey GRC, Johnston JA, Rozdilsky B. Decadron in the treatment of cerebral abscess. *Neurosurgery* 1976;45:301-10.
- Chapman ME, Sellar RJ, Whittle IR. Pyocephalus: a valuable CT finding in cerebral abscess. *Clin Radiol* 1992;45:195-7.
- Verboon-Maciolek M, Vandertop WP, Peters AC, Roord JJ, Geelen SP. Neonatal brain abscess caused by *Morganella morganii*. *Clin Infect Dis* 1995;20:471.
- Hagneese ME, Bauwens JE, Kjos B, Bowden RA. Brain abscess following marrow transplantation: experience at the Fred Hutchinson Cancer Research Center, 1984-1992. *Clin Infect Dis* 1994;19:402-8.
- Ti RD, Chu PK, Hesslink JR, Duberg A, Wiley C. Intracranial cryptococcosis in immunocompromised patients: CT and MRI findings in 29 cases. *Am J Roentgenol* 1991;156:1245-51.
- Malasky C, Reichman LB. Long-term follow-up of tuberculoma of the brain in an AIDS patient. *Chest* 1992;101:278-79.
- Burgert SJ, Classen DC, Burke JP, Blatter DD. Candidal brain abscess associated with vascular invasion: a devastating complication of vascular catheter-related candidemia. *Clin Infect Dis* 1995;21:202-5.
- Gershan WM, Rusakow LS, Henrickson KJ, Splaingard ML. Brain abscess caused by *Blastomyces dermatitidis* in a child with cystic fibrosis. *Chest* 1994;106:601-3.
- Walot I, Miller BL, Chang L, Mehringer CM. Neuroimaging findings in patients with AIDS. *Clin Infect Dis* 1996;22:906-19.
- Escobar A, Del-Brutto OF. Multiple brain abscesses from isolated cerebral mucormycosis. *J Neurol Neurosurg Psychiatr* 1990;53:431-33.
- Ohnishi K, Murata M, Kojima H, Takemura N, Tsuchida T, et al. Brain abscess due to infection with *Entamoeba histolytica*. *Am J Trop Med Hyg* 1994;51:180-2.