Balamuthia mandrillaris brain abscess successfully treated with complete surgical excision and prolonged combination antimicrobial therapy

Case report

Denis W. Spelman, M.B.B.S., M.P.H., F.R.A.C.P., F.R.C.P.A.,
Rhoda Cameron, M.B.B.S., F.R.C.P.A., Gregory Malham, M.B.Ch.B., F.R.A.C.S.,

Infectious Diseases Unit and Departments of Neurosurgery, Microbiology, and Pathology, and Dermatology Unit, The Alfred Hospital; Department of Medicine, Monash University; and Burnet Institute, Melbourne, Victoria, Australia

Amoebic encephalitis is an uncommon and usually fatal condition. This case describes successful treatment of a Balamuthia mandrillaris brain abscess using prolonged antimicrobial agents with complete excision. It illustrates the risk of dissemination from cutaneous to cerebral amoebic lesions, potential progression with corticosteroid therapy, and the prospect for curative excision. (DOI: 10.3171/2010.10.JNS10677)

Key Words • Balamuthia mandrillaris • brain abscess • free-living amoeba

Cerebral amoebic infections are uncommon and are rarely diagnosed antemortem. Recognition of the clinical scenario, appropriate diagnostic tests, and initiation of treatment is often delayed. A notable survivor is presented here to outline the clinical characteristics, investigative pathway, and operative approaches for others who may encounter these rare pathogens.

Case Report

History and Examination. This previously healthy 80-year-old woman from a rural area of Victoria, Australia, presented to our hospital with an abrasion to the dorsum of her right hand while gardening. She developed a large erythematous, violaceous, eroded plaque on the back of her right hand. This lesion was slow to heal, and a number of painless erythematous, violaceous 1–3-cm plaques and nodules began appearing more proximally over her arms. In the next 6 months, similar lesions appeared scattered asymmetrically on her torso, both arms, and buttocks.

Multiple skin biopsies were nondiagnostic, showing nonnecrotizing and nonsuppurative granulomas with a background of lymphocytes and plasma cells. Test results for bacterial, fungal, and mycobacterial stains and cultures were negative. A mycobacterial multiplex PCR test result was positive for 1 of 5 biopsy samples (in-house assay, Victorian Infectious Diseases Reference Laboratory) for an unknown species. There were no other physical symptoms or signs over an 18-month period. Other tests were nondiagnostic, including a negative Quantiferon Gold (γ-interferon release assay, Cellestis), nonreactive syphilis serology (rapid plasma reagent and enzyme immunoassay total antibody), nondetectable antinuclear and antineutrophil cytoplasmic antibodies, normal angiotensin-converting enzyme (67 U/L, reference range 12–68 U/L) and a normal serum calcium level (2.4 mmol/L). She was immunocompetent with normal results from a full blood examination.

* Abbreviation used in this paper: PCR = polymerase chain reaction.
* Drs. Doyle and Campbell contributed equally to this work.

This article contains some figures that are displayed in color online but in black and white in the print edition.
Topical corticosteroid treatment had no effect on the lesions. The patient commenced a therapeutic trial of oral corticosteroids (prednisolone 25 mg daily) because an inflammatory etiology was proposed for her rash. This was followed within weeks by an increase in the size of her skin lesions (Fig. 1). A further skin biopsy was obtained at our institution 2 weeks prior to her acute presentation.

Four weeks into her steroid therapy, she collapsed at home with 2 generalized tonic-clonic seizures. On admission to the hospital, she had no focal neurological signs, but she had postictal confusion and mild disinhibition that resolved after 48 hours. After commencing phenytoin she suffered no further seizures. Basic hematological and biochemical test results were within normal limits. An MR imaging study of her brain demonstrated a solitary lesion in the medial right frontal lobe, at the gray-white matter junction. The lesion had an irregular enhancing rim with peripheral diffusion restriction, and surrounding vasogenic edema. Empiric brain abscess treatment of benzylpenicillin, ceftriaxone, and metronidazole was commenced.

An additional MR imaging study was performed 4 days later, showing that the lesion and the surrounding edema had increased in size (Fig. 2). Histological analysis of her recent skin biopsy showed a mixed inflammatory cell infiltrate within the dermis and subcutis including numerous Langhans-type dermal giant cells. Frequent amoebic trophozoites were identified within the areas of inflammation, often within giant cells (Fig. 3). No other organisms were identified on stains for fungi, acid-fast bacilli, or bacteria.

**Operation.** A provisional diagnosis of amoebic encephalitis was made. Given the extremely poor prognosis...
of this condition, a neurosurgical assessment was sought for excision of the patient’s brain lesion. A frameless stereotactic craniotomy was performed, and the lesion was excised en masse, with a surrounding margin of normal brain tissue. A macroscopic abscess with a central necrotic core was excised en bloc and similar to her skin biopsy, amoebic trophozoites were visualized in the brain tissue (Fig. 4). An Escherichia coli lawn culture of brain tissue failed to detect any further trophozoites and Balamuthia mandrillaris was identified by PCR (Center for Disease Control and Prevention). Amoebic serology and immunofluorescence analyses were not performed.

Antimicrobial therapy was broadened within the 1st week of presentation to include intravenous pentamidine 300 mg daily, oral azithromycin 600 mg daily, oral itraconazole 200 mg twice daily, oral sulphadiazine 1.5 mg 4 times a day, and oral flucytosine 1 g 3 times a day. Corticosteroids were weaned rapidly. Intravenous pentamidine was associated with significant hypotension, which occurred again on rechallenge, and intravenous liposomal amphotericin (3 mg/kg/day) was given instead for 4 weeks intravenous therapy in total. Mild renal impairment was observed in association with liposomal amphotericin therapy. Liver enzyme dysfunction was also observed, requiring a 50% dose reduction in the sulphadiazine.

**Postoperative Course.** The patient’s postoperative course was complicated by a failure to wake, and she required intensive care for 1 week for airway support. Imaging revealed no evidence of postoperative intracranial hemorrhage. She was discharged home having made a full neurological recovery after a total of 7 weeks in the hospital and rehabilitation facility, and she was not taking antiseizure medication. The 4 oral agents were continued for 7 months in total, at which point her skin lesions and brain abscess had resolved.

She remains clinically well and stopped taking all antimicrobial agents 11 months ago. She had 1 self-limiting seizure during the period when she was not taking antimicrobial therapy, and she had no new skin or brain lesions. This seizure was attributed to postoperative scarring rather than disease recurrence.

**Discussion**

Granulomatous amoebic encephalitis caused by free-living amoebae is a rare condition that is difficult to diagnose, hard to treat, and generally fatal. Balamuthia mandrillaris has caused more than 125 confirmed cases of amoebic encephalitis, and only 4 survivors have been reported (Table 1).1,3,13

There are 4 genera of free-living amoeba associated with human infection. Naegleria fowleri tends to cause an amoebic meningoencephalitis characterized by a hemorrhagic necrotizing infection of CNS occurring in previous healthy children and young adults.5,16 Sappinia spp. have been described as a cause of brain abscess in immunocompetent hosts.2,9 Acanthamoeba spp. and Balamuthia mandrillaris, both causes of granulomatous amoebic encephalitis, are associated with immunocompromised states, and can also involve the lung and skin, including keratitis associated with contact lenses.5,7,16

These protozoa are widely distributed in the natural environment, including fresh water, soil, domestic water supplies, and air conditioning.5,6,13 Amoeba can also serve as reservoirs in the environment for pathogenic bacteria such as Legionella and Mycobacterium.6 It is biologically plausible that the positive Mycobacterium PCR in this case detected cellular components within the amoebae. Exposure to free-living amoebae is thought to be common from water and soil contact, with antibodies found in serum samples from healthy humans.5

Corticosteroid use has been associated with amoebic encephalitis.20,13 Steroids can lead to immunosuppression and could therefore potentially facilitate passage of amoebae across the blood-brain barrier.15 The concern of steroids worsening parasitic infections is biologically plausible and is supported by the temporal relationship in this patient. However, there are no other reports to date of a clear relationship between corticosteroid use and abrupt dissemination of Balamuthia infection.
TABLE 1: Comparison of reported successfully treated cases of *Balamuthia* encephalitis

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Presentation</th>
<th>Risk Factors</th>
<th>Means of Diagnosis</th>
<th>Antimicrobial Therapy</th>
<th>Op</th>
<th>Outcome</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelman et al., 2001</td>
<td>5, F</td>
<td>generalized seizures</td>
<td>immunocompetent</td>
<td>brain biopsy, IIF</td>
<td>initial: pentamidine (2 wks); fluconazole, fluconazole, sulfadiazine, clarithromycin (1.5 yrs); maintenance (&gt;2.5 yrs): fluconazole, clarithromycin</td>
<td>partial excision of 1 of 2 lesions</td>
<td>moderate performance problems in school</td>
<td>&gt;2.5 yrs</td>
</tr>
<tr>
<td>Jung et al., 2004</td>
<td>35, M</td>
<td>seizures</td>
<td>B cell lymphoma</td>
<td>biopsy only</td>
<td>relapse at 6 mos, severe neurological deficits</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gelman et al., 2001</td>
<td>64, M</td>
<td>skin lesion, later rt hemiparesis &amp; generalized seizures</td>
<td>immunocompetent</td>
<td>brain biopsy, IIF</td>
<td>biopsy only</td>
<td>excision of 1 of 2 lesions</td>
<td>complete recovery</td>
<td>6 mos</td>
</tr>
<tr>
<td>Deetz et al., 2003</td>
<td>72, F</td>
<td>focal lt-sided seizure</td>
<td>immunocompetent</td>
<td>skin/brain biopsy, PCR</td>
<td>initial: pentamidine (1 wk), then liposomal amphotericin (3 wks); fluconazole, azithromycin, itraconazole, sulfadiazine (7 mos); no maintenance</td>
<td>complete excision of solitary abscess</td>
<td>complete recovery</td>
<td>18 mos</td>
</tr>
<tr>
<td>present case</td>
<td>80, F</td>
<td>skin lesions, 18 mos later generalized seizures</td>
<td>immunocompetent</td>
<td>skin/brain biopsy, PCR</td>
<td>initial: pentamidine (1 wk), then liposomal amphotericin (unreported duration)</td>
<td>excision of 1 of 2 lesions</td>
<td>complete recovery</td>
<td>6 mos</td>
</tr>
</tbody>
</table>

* FU = follow-up; IIF = immunofluorescence; NR = not reported.

Conclusions

To our knowledge, this case is the first report in which surgical removal of the intracerebral infection was performed, resulting in a favorable outcome. While we were unable to prove that prednisolone caused disseminated *Balamuthia* infection, we observed a clear temporal relationship in the combination of excision and broad antimicrobial use that contributed to our patient's favorable outcome.

The role of surgery in *Balamuthia* infection has previously been described, mainly as a diagnostic tool. In this case, the patient underwent excision of the solitary brain abscess, which was completely removed at surgery. The exact duration needed to completely treat an amoebic brain abscess is uncertain. There are no validated biochemical markers of response to treatment. Expert opinion and previous reports indicate that surgery alone may be rarely effective. Antimicrobial recommendations are based on limited case reports of in vivo use. In vitro evidence suggests that *Balamuthia* isolates of limited case reports in vivo are less sensitive to amphotericin B compared to other amphotericins. However, amphotericin B has been used successfully in cases of cutaneous *Balamuthia* infection. Antimicrobial recommendations are based only on in vitro evidence and isolated case reports, which may not be clinically relevant. Expert opinion and previous reports indicate that surgery alone may be rarely effective.

**Table 1: Comparison of reported successfully treated cases of *Balamuthia* encephalitis**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Presentation</th>
<th>Risk Factors</th>
<th>Means of Diagnosis</th>
<th>Antimicrobial Therapy</th>
<th>Op</th>
<th>Outcome</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelman et al., 2001</td>
<td>5, F</td>
<td>generalized seizures</td>
<td>immunocompetent</td>
<td>brain biopsy, IIF</td>
<td>initial: pentamidine (2 wks); fluconazole, fluconazole, sulfadiazine, clarithromycin (1.5 yrs); maintenance (&gt;2.5 yrs): fluconazole, clarithromycin</td>
<td>partial excision of 1 of 2 lesions</td>
<td>moderate performance problems in school</td>
<td>&gt;2.5 yrs</td>
</tr>
<tr>
<td>Jung et al., 2004</td>
<td>35, M</td>
<td>seizures</td>
<td>B cell lymphoma</td>
<td>biopsy only</td>
<td>relapse at 6 mos, severe neurological deficits</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gelman et al., 2001</td>
<td>64, M</td>
<td>skin lesion, later rt hemiparesis &amp; generalized seizures</td>
<td>immunocompetent</td>
<td>brain biopsy, IIF</td>
<td>biopsy only</td>
<td>excision of 1 of 2 lesions</td>
<td>complete recovery</td>
<td>6 mos</td>
</tr>
<tr>
<td>Deetz et al., 2003</td>
<td>72, F</td>
<td>focal lt-sided seizure</td>
<td>immunocompetent</td>
<td>skin/brain biopsy, PCR</td>
<td>initial: pentamidine (1 wk), then liposomal amphotericin (3 wks); fluconazole, azithromycin, itraconazole, sulfadiazine (7 mos); no maintenance</td>
<td>complete excision of solitary abscess</td>
<td>complete recovery</td>
<td>18 mos</td>
</tr>
<tr>
<td>present case</td>
<td>80, F</td>
<td>skin lesions, 18 mos later generalized seizures</td>
<td>immunocompetent</td>
<td>skin/brain biopsy, PCR</td>
<td>initial: pentamidine (1 wk), then liposomal amphotericin (unreported duration)</td>
<td>excision of 1 of 2 lesions</td>
<td>complete recovery</td>
<td>6 mos</td>
</tr>
</tbody>
</table>

* FU = follow-up; IIF = immunofluorescence; NR = not reported.

Conclusions

To our knowledge, this case is the first report in which surgical removal of the intracerebral infection was performed, resulting in a favorable outcome. While we were unable to prove that prednisolone caused disseminated *Balamuthia* infection, we observed a clear temporal relationship in the combination of excision and broad antimicrobial use that contributed to our patient's favorable outcome.

The role of surgery in *Balamuthia* infection has previously been described, mainly as a diagnostic tool. In this case, the patient underwent excision of the solitary brain abscess, which was completely removed at surgery. The exact duration needed to completely treat an amoebic brain abscess is uncertain. There are no validated biochemical markers of response to treatment. Expert opinion and previous reports indicate that surgery alone may be rarely effective. Antimicrobial recommendations are based on limited case reports of in vivo use. In vitro evidence suggests that *Balamuthia* isolates of limited case reports in vivo are less sensitive to amphotericin B compared to other amphotericins. However, amphotericin B has been used successfully in cases of cutaneous *Balamuthia* infection. Antimicrobial recommendations are based only on in vitro evidence and isolated case reports, which may not be clinically relevant. Expert opinion and previous reports indicate that surgery alone may be rarely effective.

**Table 1: Comparison of reported successfully treated cases of *Balamuthia* encephalitis**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Presentation</th>
<th>Risk Factors</th>
<th>Means of Diagnosis</th>
<th>Antimicrobial Therapy</th>
<th>Op</th>
<th>Outcome</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelman et al., 2001</td>
<td>5, F</td>
<td>generalized seizures</td>
<td>immunocompetent</td>
<td>brain biopsy, IIF</td>
<td>initial: pentamidine (2 wks); fluconazole, fluconazole, sulfadiazine, clarithromycin (1.5 yrs); maintenance (&gt;2.5 yrs): fluconazole, clarithromycin</td>
<td>partial excision of 1 of 2 lesions</td>
<td>moderate performance problems in school</td>
<td>&gt;2.5 yrs</td>
</tr>
<tr>
<td>Jung et al., 2004</td>
<td>35, M</td>
<td>seizures</td>
<td>B cell lymphoma</td>
<td>biopsy only</td>
<td>relapse at 6 mos, severe neurological deficits</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gelman et al., 2001</td>
<td>64, M</td>
<td>skin lesion, later rt hemiparesis &amp; generalized seizures</td>
<td>immunocompetent</td>
<td>brain biopsy, IIF</td>
<td>biopsy only</td>
<td>excision of 1 of 2 lesions</td>
<td>complete recovery</td>
<td>6 mos</td>
</tr>
<tr>
<td>Deetz et al., 2003</td>
<td>72, F</td>
<td>focal lt-sided seizure</td>
<td>immunocompetent</td>
<td>skin/brain biopsy, PCR</td>
<td>initial: pentamidine (1 wk), then liposomal amphotericin (3 wks); fluconazole, azithromycin, itraconazole, sulfadiazine (7 mos); no maintenance</td>
<td>complete excision of solitary abscess</td>
<td>complete recovery</td>
<td>18 mos</td>
</tr>
</tbody>
</table>

* FU = follow-up; IIF = immunofluorescence; NR = not reported.

Conclusions

To our knowledge, this case is the first report in which surgical removal of the intracerebral infection was performed, resulting in a favorable outcome. While we were unable to prove that prednisolone caused disseminated *Balamuthia* infection, we observed a clear temporal relationship in the combination of excision and broad antimicrobial use that contributed to our patient's favorable outcome.

The role of surgery in *Balamuthia* infection has previously been described, mainly as a diagnostic tool. In this case, the patient underwent excision of the solitary brain abscess, which was completely removed at surgery. The exact duration needed to completely treat an amoebic brain abscess is uncertain. There are no validated biochemical markers of response to treatment. Expert opinion and previous reports indicate that surgery alone may be rarely effective. Antimicrobial recommendations are based on limited case reports of in vivo use. In vitro evidence suggests that *Balamuthia* isolates of limited case reports in vivo are less sensitive to amphotericin B compared to other amphotericins. However, amphotericin B has been used successfully in cases of cutaneous *Balamuthia* infection. Antimicrobial recommendations are based only on in vitro evidence and isolated case reports, which may not be clinically relevant. Expert opinion and previous reports indicate that surgery alone may be rarely effective.

**Table 1: Comparison of reported successfully treated cases of *Balamuthia* encephalitis**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Presentation</th>
<th>Risk Factors</th>
<th>Means of Diagnosis</th>
<th>Antimicrobial Therapy</th>
<th>Op</th>
<th>Outcome</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelman et al., 2001</td>
<td>5, F</td>
<td>generalized seizures</td>
<td>immunocompetent</td>
<td>brain biopsy, IIF</td>
<td>initial: pentamidine (2 wks); fluconazole, fluconazole, sulfadiazine, clarithromycin (1.5 yrs); maintenance (&gt;2.5 yrs): fluconazole, clarithromycin</td>
<td>partial excision of 1 of 2 lesions</td>
<td>moderate performance problems in school</td>
<td>&gt;2.5 yrs</td>
</tr>
<tr>
<td>Jung et al., 2004</td>
<td>35, M</td>
<td>seizures</td>
<td>B cell lymphoma</td>
<td>biopsy only</td>
<td>relapse at 6 mos, severe neurological deficits</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gelman et al., 2001</td>
<td>64, M</td>
<td>skin lesion, later rt hemiparesis &amp; generalized seizures</td>
<td>immunocompetent</td>
<td>brain biopsy, IIF</td>
<td>biopsy only</td>
<td>excision of 1 of 2 lesions</td>
<td>complete recovery</td>
<td>6 mos</td>
</tr>
<tr>
<td>Deetz et al., 2003</td>
<td>72, F</td>
<td>focal lt-sided seizure</td>
<td>immunocompetent</td>
<td>skin/brain biopsy, PCR</td>
<td>initial: pentamidine (1 wk), then liposomal amphotericin (3 wks); fluconazole, azithromycin, itraconazole, sulfadiazine (7 mos); no maintenance</td>
<td>complete excision of solitary abscess</td>
<td>complete recovery</td>
<td>18 mos</td>
</tr>
</tbody>
</table>

* FU = follow-up; IIF = immunofluorescence; NR = not reported.

Conclusions

To our knowledge, this case is the first report in which surgical removal of the intracerebral infection was performed, resulting in a favorable outcome. While we were unable to prove that prednisolone caused disseminated *Balamuthia* infection, we observed a clear temporal relationship in the combination of excision and broad antimicrobial use that contributed to our patient's favorable outcome.

The role of surgery in *Balamuthia* infection has previously been described, mainly as a diagnostic tool. In this case, the patient underwent excision of the solitary brain abscess, which was completely removed at surgery. The exact duration needed to completely treat an amoebic brain abscess is uncertain. There are no validated biochemical markers of response to treatment. Expert opinion and previous reports indicate that surgery alone may be rarely effective. Antimicrobial recommendations are based on limited case reports of in vivo use. In vitro evidence suggests that *Balamuthia* isolates of limited case reports in vivo are less sensitive to amphotericin B compared to other amphotericins. However, amphotericin B has been used successfully in cases of cutaneous *Balamuthia* infection. Antimicrobial recommendations are based only on in vitro evidence and isolated case reports, which may not be clinically relevant. Expert opinion and previous reports indicate that surgery alone may be rarely effective.
this case. We recommend avoiding steroids in clinical settings where amoebic infection may be possible.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Doyle, Campbell, Fuller. Acquisition of data: Doyle, Campbell, Fuller, Cameron, Malham, Lewin. Analysis and interpretation of data: Doyle, Campbell, Fuller, Spelman. Drafting the article: Doyle, Campbell. Critically revising the article: Fuller, Spelman, Cameron, Gin, Lewin. Reviewed final version of the manuscript and approved it for submission: all authors.

Acknowledgment

The authors thank Dr. Harsha Sheorey for assistance in the microbiological identification in this case.

References


Manuscript submitted June 9, 2010. Accepted October 12, 2010. Portions of this work were presented as proceedings of the 50th Interscience Conference on Antimicrobial Agents and Chemotherapeutics (ICAAC), Boston, Massachusetts, September 13, 2010. Please include this information when citing this paper: published online November 12, 2010; DOI: 10.3171/2010.10.JNS10677. Address correspondence to: Joseph S. Doyle, M.B.B.S., M.Sc., Infectious Diseases Registrar, Victorian Infectious Diseases Service, Royal Melbourne Hospital, Grattan Street, Parkville, Victoria, 3052, Australia. email: joseph.doyle@alumni.unimelb.edu.au.