response by rhabdomyosarcoma in children: Report of a retrospective case study. Clin Nucl Med 2006;31:394–397.
4. Go RS, Wester SM. Immunophenotypic and molecular features, clinical outcomes, treatments and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma. Cancer 2004;101:1404–1413.
5. Yim JH, Kim M-Y, Kim HO, et al. Subcutaneous panniculitis-like T-cell lymphoma in a 26-month-old child with a review of the literature. Pediatr Dermatol 2006;23:537–540.
6. Windsor R, Stiller C, Webb D. Peripheral T-cell lymphoma in childhood: Population-based experience in the United Kingdom over 20 years. Pediatr Blood Cancer 2008;50:784–787.
7. Hoque SR, Child FJ, Whittaker SJ, et al. Subcutaneous panniculitis-like T-cell lymphoma: A clinicopathological, immunophenotypic and molecular analysis of six patients. Br J Dermatol 2003; 148:516–525.
8. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: Definition, classification, and prognostic factors: An EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 2008;111:838–845.
9. Bregman SG, Yeaney GA, Greig BW, et al. Subcutaneous panniculitic T-cell lymphoma in a cardiac allograft recipient. J Cutan Pathol 2005;32:366–370.
10. Hung GD, Chen YH, Chen DY, et al. Subcutaneous panniculitis-like T-cell lymphoma presenting with hemophagocytic lymphohistiocytosis and skin lesions with characteristic high-resolution ultrasonographic findings. Clin Rheumatol 2007;26:775–778.
11. Shen L, Alam-Fotias S, Mansberg R, et al. Subcutaneous panniculitis-like T cell lymphoma demonstrated on Gallium-67 scintigraphy. Clin Nucl Med 2005;30:500–502.
12. Kumar R, Xiu Y, Zhuang HM, et al. 18F-fluorodeoxyglucose-positron emission tomography in evaluation of primary cutaneous lymphoma. Br J Dermatol 2006;155:357–363.
13. Kako S, Izutsu K, Ota Y, et al. FDG-PET in T-cell and NK-cell neoplasms. Anal Oncol 2007;18:1685–1690.

# Management of Brain Abscesses in Children Treated for Acute Lymphoblastic Leukemia

**Herwig Lackner, MD,[1]* Petra Sovinz, MD,[1] Martin Benesch, MD,[1] Freyja Smolle-Jüttner, MD,[2] Michael Mokry, MD,[3] Wolfgang Schwinger, MD,[1] Andrea Moser, MD,[1] and Christian Urban, MD[1]**

Brain abscesses in children with leukemia or other malignancies are rare and potentially fatal. We report on four children who developed brain abscesses during treatment for acute lymphoblastic leukemia (ALL). All patients received multimodal broad-spectrum antibiotic therapy and liposomal amphotericin-B in combination with hyperbaric oxygen. First-line antimicrobial treatment was modified when a causative organism was isolated. All four patients survived, with two patients showing complete resolution of neurological and MRI abnormalities and with two patients still having residual lesions. To date, all patients are in remission with three patients still receiving antileukemic therapy. Brain abscesses can be successfully managed by a multimodality approach even in severely immunocompromised cancer patients. Pediatr Blood Cancer 2009;52:408–411. © 2008 Wiley-Liss, Inc.

**Key words:** acute lymphoblastic leukemia; brain abscesses; children; management

## INTRODUCTION

Brain abscesses are rare in immunocompromised patients, and mortality rates exceeding 90% have been reported [1–8]. Only few cases of brain abscesses in children treated for acute lymphoblastic leukemia (ALL) have been reported [9–14]. Since prognosis was very dismal and little information about the appropriate management of this complication was given, we are reporting on the successful management of four children with ALL, who developed brain abscesses during antileukemic therapy.

## CASE REPORTS

From January 2001 to February 2008, 68 patients were diagnosed with ALL at our institution. These children were treated according to the international treatment protocols ALL BFM 2000 or INTERFANT 06. A written informed consent was obtained from parents or their legal guardians. Supportive care included insertion of a central venous line, infection prophylaxis with oral amphotericin B, trimethoprim/sulphametoxazole (4/20 mg/kg, 4 times weekly), and broad spectrum antibiotics or blood products if necessary. Four children (three males and one female) developed brain abscesses during antileukemic therapy. Their ages at diagnosis of ALL were 15, 2, 4, and 0.08 years, respectively. Routine cultures of the cerebrospinal fluid (CSF) were negative in all cases. Brain abscesses occurred during induction therapy in three patients and during reinduction therapy in one patient. At onset of neurologic symptoms, lumbar puncture and magnetic resonance imaging (MRI) were performed [15]. When diagnosis of brain abscesses was confirmed, primary treatment included empirical broad spectrum antibiotics and liposomal amphotericin B (LAmB). Additionally, all children underwent treatment with hyperbaric oxygen (HBO) as previously described [16,17]. Primary treatment

Additional Supporting Information may be found in the online version of this article.

[1]Division of Pediatric Hematology/Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria; [2]Division of Thoracic and Hyperbaric Surgery, Medical University of Graz, Graz, Austria; [3]Department of Neurosurgery, Medical University of Graz, Graz, Austria

*Correspondence to: Herwig Lackner, Division of Pediatric Hematology/Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Auenbruggerplatz 30, A-8036 Graz, Austria. E-mail: herwig.lackner@meduni-graz.at

Received 2 July 2008; Accepted 12 September 2008


DOI 10.1002/pbc.21814
Published online 6 November 2008 in Wiley InterScience (www.interscience.wiley.com)

was individually adapted according to the microbiological test results.

Hemiparesis was the first neurologic symptom in all patients. Additionally, one patient developed facial nerve palsy and aphasia and one patient developed seizures. Diagnosis of brain abscesses was established by MRI with the number of lesions ranging between 2 and 8 (Table I). Analysis of CSF revealed normal results in two patients and elevation of protein and mild pleocytosis in the two other patients. A microbiological diagnosis was made by polymerase chain reaction (PCR) for three of the four cases. The assays were commercially available and/or established assays performed at a reference laboratory. The detected causative agents were *Acanthamoeba* (patient 2), *Toxoplasma gondii* (patient 3), and *Aspergillus fumigatus* (patient 4). In one patient (patient 1), neither analysis of CSF nor biopsy was successful (Table II). Antimicrobial therapy included fluconazole, pentamidine, and miltefosine in the patient with Acanthamoeba as previously published [18,19]. Trimethoprim/sulphametoxazole in a higher, therapeutic dosage (15/75 mg/kg/daily) was given to the patient with *T. gondii*. Posaconazole (8 mg/kg twice daily) and voriconazole (4 mg/kg twice daily) were given simultaneously to the patient with *A. fumigatus* to enhance antifungal activity of LAmB. Antileukemic treatment was temporarily withheld for 19, 14, 10, and 20 days, respectively.

Two patients (patients 1 and 2) had a complete clinical as well as radiologic recovery from their brain abscesses. Two others showed improvement of both clinical symptoms and MRI findings; however, in addition to mild residual neurological deficits, follow-up MRIs disclosed residual lesions with decreased enhancement. Patient 4 currently receives continuous antimicrobial treatment for *A. fumigatus*. One patient (patient 1) had a leukemic relapse 1 year after the end of antileukemic treatment and was retreated according to the ALL-REZ BFM 2002 protocol [20]. He achieved second remission, finished antileukemic treatment 1 year ago and is in continuous second remission 4 years from his relapse. The remaining three patients are in first remission and still being treated for their leukemia.

## DISCUSSION

Brain abscesses are a rare and devastating complication in children treated for ALL. Carrying out a PubMed search we found only 13 cases reported so far, most of them single case reports [9–14,18]. Fungi, mainly *Aspergillus*, were the causative organisms in 12 of the 13 patients, however, less common causative agents (e.g., *Listeria or Cryptococcus*) are increasingly being documented as occasional pathogens [9,10,21]. Multimodal therapy included systemic antimycotic and antibiotic therapy in all reported patients and surgical resection of the lesions in six patients. Nine patients survived, whereas four patients died.

Our series of four patients with brain abscesses during antileukemic induction or reinduction therapy reports on a multimodal and targeted treatment approach including HBO therapy in this setting. In addition, it reports the involvement of two unusual organisms (an *Acanthamoeba* species and *T. gondii*) in brain abscesses in ALL patients. Patient 2 represents the rare case of an infection with *Acanthamoeba*. The child lives in a rural region and uses water from a private well however, analysis of the water was negative for *Acanthamoeba*. Patient 3 was positive for *T. gondii* and responded well to trimethoprim/sulphametoxazole in an increased dosage. Patient 4 was diagnosed with *A. fumigatus* by PCR and

**TABLE I. Brain Abscesses in Four Children With ALL: Patient Characteristics, Oncologic Pretreatment, and Symptoms**

| Patient | Sex | Age at diagnosis of ALL (years) | Treatment protocol | Oncologic status at onset of neurologic symptoms | Duration of neutropenia (ANC $< 1 \times 10^9$/L) prior to the brain abscesses (days) | Neurologic symptoms | MRI (number of lesions) |
|---|---|---|---|---|---|---|---|
| 1 | m | 15 | ALL BFM 2000 | Reinduction (protocol II/DXM) | 17 | Right hemiparesis facial nerve palsy, aphasia | 4 |
| 2 | m | 2 | ALL BFM 2000 | Induction (protocol I/DXM) | 2 | Left hemiparesis | 8 |
| 3 | m | 4 | ALL BFM 2000 | Induction (protocol I/DXM) | 7 | Right hemiparesis seizures | 3 |
| 4 | f | 0.08 | INTERFANT 06 | Induction /DXM | 10 | Right hemiparesis | 2 |

ALL, acute lymphoblastic leukemia; DXM, dexamethasone; ANC, absolute neutrophil count.

**TABLE II. Brain Abscesses in Four Children With ALL: Microbiological Diagnosis, Treatment, Outcome**

| Patient | CSF | Biopsy/histology | Causative agent | Treatment | Duration of antimicrobial therapy (days) | Delay of antileukemic therapy (days) | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | Protein ↑ (75 mg/dl) | Dense granulocytic infiltration | Not detected | Antibiotics (meropenem, fosfomycin, metronidazole) LAmB, HBO | 61 | 19 | Relapse → ALL-REZ BFM 2002 second remission complete neurologic recovery |
| 2 | Protein ↑ (60 mg/dl) pleocytosis (293 cells/mm$^3$ granulocytes and monocytes) | n.d. | *Acanthamoeba* (CSF: PCR+) | Antibiotics, LAmB, HBO, fluconazole, pentamidine, miltefosine | 36 | 14 | First remission complete neurologic recovery still on antileukemic therapy |
| 3 | Normal | n.d. | *Toxoplasma gondii* (CSF: PCR+) | Antibiotics, LAmB, HBO, trimethoprim/ sulphametoxazole | 56 | 10 | First remission neurologic improvement still on antileukemic therapy |
| 4 | Normal | Necrosis and granulocytes | *Aspergillus fumigatus* (biopsy: PCR+) | Antibiotics, LAmB, HBO, posaconazole, voriconazole | >180 (still on therapy) | 20 | First remission neurologic improvement still on antileukemic therapy + LAmB, posaconazole, voriconazole |

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; HBO, hyperbaric oxygen therapy; LAmB, liposomal amphotericin B; n.d., not done.

confirmed by repeatedly positive galactomannan tests, albeit all cultures were negative. Other aspergillus localizations (e.g., lungs or sinuses) were not detected. The Supplemental Figure demonstrates the response to multimodal treatment in patient 1. The appearance of the images did not substantially differ from one patient to the other. An aggressive diagnostic approach including lumbar puncture and/or biopsy of a representative brain lesion is warranted to identify the causative organism and to start a tailored treatment [10,14,22].

Treatment of brain abscesses with empiric antibiotics that include an antifungal agent should be started immediately. Subsequently, an extended targeted antimicrobial treatment can be added when a specific pathogen has been identified [1]. Prolonged combined or sequential antifungal therapy including LAmB and/or the new azoles has been shown to be effective and feasible, even in the setting of antileukemic treatment [4,8,10,18]. Neurosurgical excision of the abscesses should be considered whenever possible [1]. In cases with multiple or deep seated lesions, a surgical approach beyond initial diagnostic biopsy is not justified. In our study, all patients had multiple lesions, and surgical resection without persisting neurologic sequelae was not considered to be possible. Nevertheless, all patients were successfully managed with conservative antibiotic and/or antimycotic treatment. There are reports describing HBO therapy in children with brain abscesses and osteonecroses [16,17]. Potential mechanisms for its benefit might be a positive effect on cerebral blood flow and a direct antimicrobial effect of oxygen, especially on anaerobes [16]. The future role of HBO therapy as additional supportive treatment option in patients with ALL and brain abscesses remains to be established.

In summary, several suggestions can be given on how to approach and manage brain abscesses in children with ALL. First, brain abscesses can occur as a complication of antileukemic treatment, and physicians should be aware of this rare and life-threatening situation. Second, an aggressive diagnostic approach including lumbar puncture and/or biopsy is necessary to detect the causative organism and to start targeted antimicrobial therapy. Third, prolonged empirical administration of antibiotics and antifungals is always necessary and feasible even in the setting of ongoing antileukemic therapy. Fourth, the delay of antileukemic treatment should be as short as possible to avoid leukemic relapse. Fifth, a surgical approach should be considered. However, in children with unresectable lesions, conservative treatment including antibiotics and antimycotics might be sufficient to induce regression of brain abscesses. More clinical data describing the clinical course and the management of children with ALL and brain abscesses should be collected in order to establish definitive management guidelines.

## REFERENCES

1. Coleman JM, Hogg GG, Rosenfeld JV, et al. Invasive central nervous system aspergillosis: Cure with liposomal amphotericin B, itraconazole, and radical surgery-case report and review of the literature. Neurosurgery 1995;36:858–863.
2. Erduran E, Yildiran A, Gedik Y. Multiple fungal brain abscess in a child with acute myeloblastic leukemia. Pediatr Hematol Oncol 1998;15:463–466.
3. Mahlknecht U, von Lintig F, Mertelsmann R, et al. Successful treatment of disseminated central nervous aspergillosis in a patient with acute myeloblastic leukemia. Leuk Lymphoma 1997;27:191–194.

4. Pagano L, Caira M, Falcucci P, et al. Fungal CNS infections in patients with hematologic malignancy. Expert Rev Anti Infect Ther 2005;3:775–785.
5. Sakai C, Iuchi T, Ishii A, et al. Bacillus cereus brain abscesses occurring in a severely neutropenic patient: Successful treatment with antimicrobial agents, granulocyte colony-stimulating factor and surgical drainage. Intern Med 2001;40:654–657.
6. Sashida G, Ishii Y, Takaku T, et al. Brain abscess in acute myeloid leukemia. Intern Med 2005;44:772.
7. Tweddle DA, Graham JC, Shankland GS, et al. Cerebral candidiasis in a child 1 year after leukaemia. Br J Haematol 1998;125:795–797.
8. Wandroo F, Stableforth P, Hasan Y. Aspergillus brain abscess in a patient with acute myeloid leukaemia successfully treated with voriconazole. Clin Lab Haematol 2006;28:130–133.
9. Al-Mohsen Z, Sutton DA, Sigler L, et al. Acrophialophora fusispora brain abscess in a child with acute lymphoblastic leukemia: Review of cases and taxonomy. J Clin Microbiol 2000; 38:4569–4576.
10. Antunes NL, Hariharan S, DeAngelis LM. Brain abscess in children with cancer. Med Pediatr Oncol 1998;31:19–21.
11. Athanassiadou F, Tragiannidis A, Papageorgiou T, et al. Fungal brain abscesses in leukemia. Indian Pediatr 2006;43:991–994.
12. Henze G, Aldenhoff P, Stephani U, et al. Successful treatment of pulmonary and cerebral aspergillosis in an immunosuppressed child. Eur J Pediatr 1982;138:263–265.
13. Khattry N, Wadhwa J, Singh D, et al. Brain abscess during induction in acute lymphoblastic leukemia: A case report. Leuk Lymphoma 2004;45:1079–1080.
14. Ng A, Gadong N, Kelsey A, et al. Successful treatment of aspergillus brain abscess in a child with acute lymphoblastic leukemia. Pediatr Hematol Oncol 2000;17:497–504.
15. Gabelmann A, Klein S, Kern W, et al. Relevant imaging findings of cerebral aspergillosis on MRI: A retrospective case-based study in immunocompromised patients. Eur J Neurol 2007;14:548–555.
16. Kurschel S, Mohia A, Weigl V, et al. Hyperbaric oxygen therapy for the treatment of brain abscess in children. Childs Nerv Syst 2006; 22:38–42.
17. Lackner H, Benesch M, Moser A, et al. Aseptic osteonecrosis in children and adolescents treated for hemato-oncologic diseases: A 13-year longitudinal observational study. J Pediatr Hematol Oncol 2005;27:259–263.
18. Walochnik J, Duchene M, Seifert K, et al. Cytotoxic activities of alkylphosphocholines against clinical isolates of Acanthamoeba spp. Antimicrob Agents Chemother 2002;46: 695–701.
19. Seijo Martinez M, Gonzalez-Mediero G, Santiago P, et al. Granulomatous amebic encephalitis in a patient with AIDS: Isolation of acanthamoeba sp. group II from brain tissue and successful treatment with sulfadiazine and fluconazole. J Clin Microbiol 2000;38:3892–3895.
20. Kirschner-Schwabe R, Lottaz C, Tödling J, et al. Expression of late cell cycle genes and an increased proliferative capacity characterize very early relapse of childhood acute lymphoblastic leukemia. Clin Cancer Res 2006;12:4553–4561.
21. Viscoli C, Garaventa A, Ferrea G, et al. Listeria monocytogenes brain abscesses in a girl with acute lymphoblastic leukaemia after late central nervous system relapse. Eur J Cancer 1991;27:435–437.
22. Sterba J, Prochazka J, Ventruba J, et al. Successful treatment of aspergillus brain abscess in a child with acute lymphoblastic leukemia and liver failure. Pediatr Hematol Oncol 2005;22:649–655.

# Transient Myeloproliferation Mimicking JMML Associated With Parvovirus Infection of Infancy

**Nidhi Gupta, MD,[1] Ritu Gupta, MD, DNB,[1]* and Sameer Bakhshi, MD[2]**

We report a 2-month-old infant with Parvovirus B19 infection presenting as transient myeloproliferation resembling juvenile myelomonocytic leukemia (JMML). Patient history, physical examination, and laboratory findings were suggestive of JMML. On viral serology, raised IgM and IgG titers for Parvovirus B19 infection were found in the absence of giant proerythroblasts and viral inclusions in the erythroid precursors. Follow-up showing a decrease in viral titers suggested parvovirus infection as an etiological factor for the development of myeloproliferative features. This case highlights the importance of viral serology in work-up myeloproliferative disorders of infancy and childhood. Pediatr Blood Cancer 2009;52:411–413. © 2008 Wiley-Liss, Inc.

**Key words:** juvenile myelomocytic leukemia; myeloproliferation; parvovirus

## INTRODUCTION

Parvovirus B19 is a highly contagious single stranded DNA virus, which has a particular tropism for erythroid precursors. It is the causative agent for a spectrum of diseases in humans and its hematological manifestation are usually in the form of an acute or chronic red blood cell aplasia [1]. Most Parvovirus B19 infections in immunocompetent patients are typically self-limited, often asymptomatic and last for only 2–3 weeks but immunocompromised patients often develop anemia as they are unable to mount a neutralizing anti-viral antibody response, which is needed to clear the virus effectively [2]. In addition, patients with underlying chronic hemolytic disorders often develop transient aplastic crisis

[1]Laboratory Oncology Unit, Dr. B. R. Ambedkar Institute Rotary Cancer Hospital (Dr. BRAIRCH), All India Institute of Medical Sciences (AIIMS), New Delhi, India; [2]Department of Medical Oncology, Dr. BRAIRCH, All India Institute of Medical Sciences (AIIMS), New Delhi, India

*Correspondence to: Ritu Gupta, Assistant Professor, Laboratory Oncology Unit, Dr. BRAIRCH, All India Institute of Medical Sciences, New Delhi 110029, India. E-mail: drritugupta@gmail.com; rituajay97@hotmail.com

Received 17 August 2008; Accepted 30 September 2008


DOI 10.1002/pbc.21842
Published online 6 November 2008 in Wiley InterScience (www.interscience.wiley.com)