

Intraventricular amphotericin for absidiomycosis in an immunocompetent child

Lilian LY Tsung 曾莉茵
XL Zhu 朱獻倫
Winnie CW Chu 朱昭穎
David TF Sun 孫天峰
KL Cheung 張錦流
TF Leung 梁廷勳

Brain abscesses are uncommon in children. We report a 3-year-old, previously healthy and immunocompetent boy, with an *Absidia* brain abscess. He presented with decreased sensorium and status epilepticus. The brain abscess was detected using cranial computed tomography and magnetic resonance imaging, and the diagnosis was confirmed with pus and brain tissue cultures. The patient responded to surgical drainage with concomitant intravenous and intraventricular amphotericin B.

Introduction

Brain abscesses are usually caused by pyogenic bacteria and are uncommon in children. Fungal infections, such as zygomycosis, are rarely responsible for brain abscesses. Zygomycosis is associated with a mortality rate higher than 50%. *Absidia corymbifera* is one of the least-reported pathogens in the Mucorales order and is responsible for less than 3% of infections caused by zygomycoses. To our knowledge, about 30 cases of *Absidia* infection have been reported in the literature¹ and all were in patients with underlying immunodeficiencies. There is no useful diagnostic marker for absidiomycosis, and the cerebrospinal fluid (CSF) culture is unhelpful in most cases. A histopathological diagnosis is needed in 40 to 70% of biopsy-proven cases. Typically, mucormycosis appears as large, broad, ribbon-like, non-septate hyphae with right-angled branching. Vascular invasion leads to infarction and septic embolism. Patients with infected ventriculo-peritoneal shunts and localised infections of the head and neck region such as otitis media, mastoiditis, and paranasal sinusitis are at risk of brain abscesses. Other predisposing factors include congenital heart disease, low birth weight, and primary (eg humoral and phagocytic immune defects) and secondary (eg acute leukaemia and organ transplantation) immunodeficiencies. We describe the first case of a young immunocompetent child with an isolated *Absidia* brain abscess.

Case report

A 3-year-old previously healthy Chinese boy, with non-consanguineous parents, who lived in Fujian, had a 5-day history of profuse watery diarrhoea. He was initially admitted to a hospital in Fujian for intravenous antibiotics and fluid resuscitation in December 2003. His scalp veins were used for venous access. He developed epilepsy and hypotension 1 week after the onset of diarrhoea, neither of which resolved. The patient's family brought him to Hong Kong for medical treatment of his refractory hypotension and status epilepticus. He was admitted to the paediatric intensive care unit in our teaching hospital. On admission his Glasgow Coma Scale (GCS) score was 8/15 and temperature was 38°C. He was placed on a ventilator immediately and given dopamine and dobutamine for inotropic support. His initial circulating leukocyte count was $12.3 \times 10^9/L$, and plasma C-reactive protein (CRP) level was 6.2 mg/L (reference level, <9.9 mg/L). His electroencephalographic features were compatible with generalised encephalopathy, and his echocardiogram revealed normal systolic cardiac function and no vegetation. An urgent non-contrast cranial computed tomographic (CT) scan showed generalised cerebral oedema and a hypodense area over the left parietal region, but the ventricles were not dilated. A magnetic resonance image of the brain performed on the following day showed multiple T2 signal changes in addition to the left parietal lesion, and diffuse meningeal contrast enhancement (Fig a). A magnetic resonance venogram was normal. Lumbar puncture was not performed on admission because his condition was too unstable. In view of these findings, the child was treated for meningo-encephalitis and given intravenous vancomycin, cefotaxime, and acyclovir.

On day 4 this boy developed a decerebrate posture. His GCS score deteriorated to 5/15, and his pupils were unequal in size. His seizures could only be controlled by intravenous phenobarbitone, topiramate, thiopentone, and a midazolam infusion (10 µg/kg/min). His CRP level increased to 12.3 mg/L. On day 5, a left parietal open brain biopsy and

Key words
Absidia; Amphotericin B; Brain abscess;
Mucormycosis

Hong Kong Med J 2010;16:137-40

The Chinese University of Hong Kong,
Prince of Wales Hospital, Shatin, Hong
Kong:

Department of Paediatrics
LLY Tsung, MRCPCH

KL Cheung, FRCPCH

TF Leung, MD, FRCPCH

Division of Neurosurgery, Department of
Surgery

XL Zhu, FRCS

DTF Sun, FRCS

Department of Diagnostic Radiology and
Organ Imaging

WCW Chu, MD, FRCS

Correspondence to: Dr LLY Tsung
Email: liliantsung@cuhk.edu.hk

為一名患有犁頭霉菌病的免疫力正常孩童施用腦室內兩性霉素

腦膿腫在孩童很罕見。本文報告一名過往健康並免疫力正常的3歲男孩患有犁頭霉菌腦膿腫的病例。男孩病發時意識下降及出現持續癲癇。顱內斷層照相及磁共振成像，以及後來的膿及腦組織培養均確診病人患有腦膿腫，遂以施行靜脈及腦室內兩性霉素替病人作外科引流治療。

right frontal burr hole with intraventricular catheter insertion was performed. The brain was found to be oedematous with pus in the sulci (Fig b). A pathological examination of the biopsy found evidence of abscess formation with tissue debris, dense granulomas and giant cells. Fungus was seen and this was confirmed by culture to be *Absidia* (*Mucor*, *Rhizopus*). Cerebrospinal fluid taken from the ventricle did not reveal any pathogens or leukocytosis, and serial blood and urine cultures were negative. Intravenous metronidazole and amphotericin B (1 mg/kg/day) were then added to his treatment. The child had persistent swinging fever and his CRP level increased to 130 mg/L. 5-Flucytosine (400 mg/m²/dose) was also commenced. He continued to deteriorate despite a second operation on day 7 for debridement of his brain abscess. Despite the addition of adrenaline to maintain his blood pressure, he developed cardiac arrest on day 10 but was successfully resuscitated.

In view of his uncontrollable *Absidia* brain abscess, the parents gave their informed written consent to have their child started with alternate-day intraventricular amphotericin B (0.5 mg dissolved in 3 mL of 5% dextrose) injections administered aseptically via a 25-gauge needle. Three millilitres of CSF were drained for culture before each injection. An Ommaya reservoir was inserted on day 21 to permit continuing intraventricular amphotericin treatment. After eight doses of intraventricular amphotericin, his CRP level dropped from its peak of 211 mg/L (day 13) to 5.8 mg/L (day 26). His state of consciousness also improved markedly, and he could cry and fix visually on his mother. A cranial CT scan showed dilated lateral ventricles but a smaller brain abscess and lesser meningeal enhancement and cerebral oedema. He was transferred to a general paediatric ward on day 37. In total, he was treated with 32 doses of intraventricular amphotericin and 3 months of intravenous antifungals (amphotericin and 5-flucytosine). Serial CT scans showed his brain abscess slowly resolving, and his plasma CRP level remained normal.

This boy underwent extensive immunological assessments to look for an underlying immunodeficiency (Table) that might have led to this opportunistic infection. He had a raised

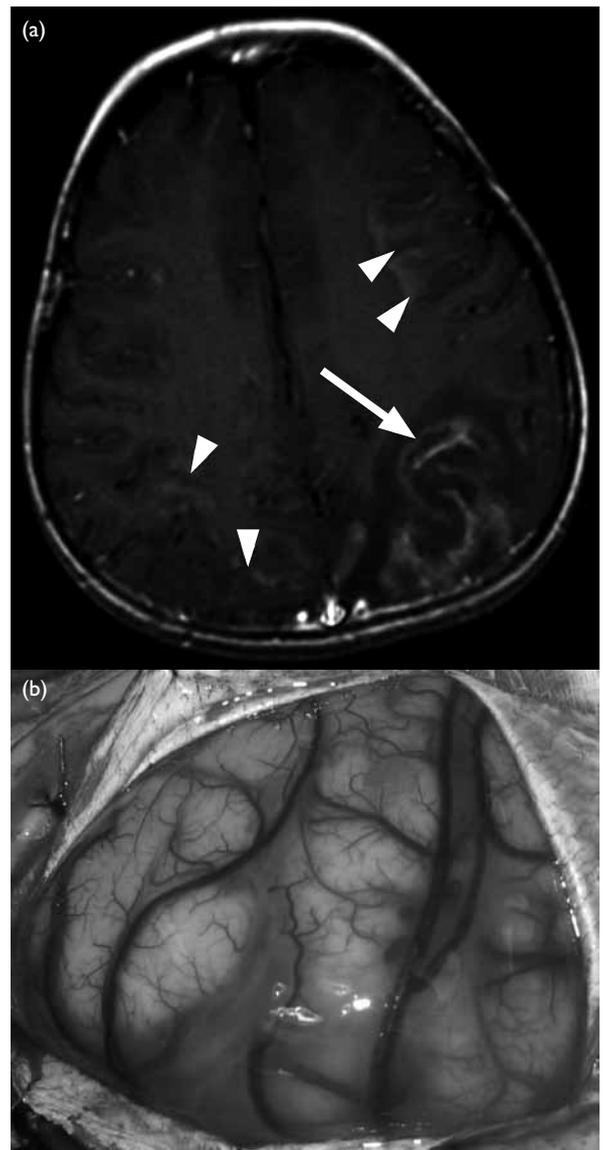


FIG. (a) Post-contrast T1-weighted magnetic resonance brain image showing a focal heterogeneous enhancing lesion at the left posterior parietal region (white arrow), which is confirmed to be a fungal abscess at biopsy. There is also diffuse meningeal enhancement (white arrowheads) in the left frontal region and right posterior parietal region. (b) Photograph of oedematous brain with pus in the sulci during the operation on day 5

percentage of circulating T-lymphocyte subsets, with his CD3+ cells, CD4+ cells, and CD8+ cells being 78% (reference range, 56-68%), 49% (29-40%), and 26% (19-25%) respectively, whereas his natural killer (CD16/56+) cell percentage was normal (13%; 9-19%). Although his circulating B-lymphocytes (CD19+) percentage was reduced (6%; 18-28%), his serum total immunoglobulin (G, A and M) concentrations were normal. He also had protective antibodies to childhood vaccines (hepatitis B, mumps, measles, rubella and poliomyelitis types 1-3), but was seronegative for the human immunodeficiency virus. His circulating phagocyte and lymphocyte functions

were also normal. Radiographs of his paranasal sinuses, nasal endoscopy, thoracic CT and abdominal ultrasound scans did not reveal any focus of *Absidia* infection. He was discharged 5 months later, and continued neurorehabilitation for right hemiplegia and developmental impairment. Over the past few years, the child has had no major infections and has thrived despite his neurological deficits. It is unlikely that the child is suffering from any primary immunodeficiency. At his latest follow-up in the clinic his growth was following the 10th centile line, despite his right hemiplegia. He could walk with support and could express himself in simple sentences.

Discussion

Zygomycosis (formerly called mucormycosis) refers to invasive infection caused by moulds from the Mucorales order. Common clinical isolates include the genera of *Absidia*, *Mucor*, *Rhizomucor*, or *Rhizopus*. They are ubiquitous fungi found in decaying fruits, soils, plants, and in the air. Zygomycosis frequently favours the sinuses, brain, or lungs as sites of infection. This infection can also manifest in the gastro-intestinal tract, skin and in other organ systems through inoculation of spores in the air. They usually cause opportunistic infections in patients with immunodeficiencies such as those caused by leukaemia, severe burns, transplantation, diabetes, and prematurity, but can, rarely, also cause infection in hosts with normal immunity.² After invading the host, the fungi proliferate quickly and invade the perivascular structures causing emboli, infarction, and necrosis and then spread through the bloodstream. Systemic factors like acidosis and prolonged use of antibiotics will facilitate its spread. A review of 929 cases of zygomycosis found diabetes mellitus and haematological malignancy to be the most important risk factors, occurring in over 50% of cases.³ Host factors for this infection may be different for adults and children.

Absidia brain abscess are rare and usually fatal. Only two patients, with lung transplantation and burns, have reportedly been treated successfully.^{1,4,5} In our case, extensive immunological investigations failed to find evidence of an underlying immunodeficiency. The child presented with profuse watery diarrhoea before his hospitalisation in Hong Kong, so we have postulated that the aggressive use of antibiotics coupled with the breakdown of the gastro-intestinal mucosa during severe diarrhoea may have led to mucormycosis in this child. Other possibilities include a soft tissue infection in the scalp due to infected scalp vein infusions and the administration of intravenous fluids or drugs that might have been contaminated by fungi. Several local cases of gastro-intestinal rhizopus infection in immunocompromised patients were caused by

TABLE. Summary of neutrophil and lymphocyte functions*

Investigation	Results	Reference range
Neutrophils (x 10⁹/L)		
Absolute neutrophil count in PB	5.1	1.5-8.5
Myeloperoxidase staining	Positive	-
Nitroblue tetrazolium test (%)		
No stimulation	0	<11
Following <i>Escherichia coli</i> endotoxin stimulation	58	>30
Following PMA stimulation	95	>82
Candida killing (%)	29	18-34
Phagocytic index	4.3	2.1-5.1
Chemotaxis (µm)		
ZAS	1082	440-1870
FMLP	1047	600-1550
Leukocyte adhesion glycoprotein CD11b (%)	99.5	>98
Lymphocytes		
Absolute lymphocyte count in PB (x 10 ⁹ /L)	1.8	1.5-7.0
In-vitro lymphoproliferative assays (cpm/10 ⁶ cells)		
Unstimulated	967	<1500
Phytohaemagglutinin	47 033	>40 900
Concanavalin A	26 420	>21 600
Pokeweed mitogen	11 547	>9700

* cpm denotes counts per minute, FMLP N-formyl-methionyl-leucyl-phenylalanine, PB peripheral blood, PMA phorbol myristate acetate, and ZAS zymosan-activated serum

contaminated allopurinol tablets.⁶

Nowadays, positron emission tomography/computed tomography is the modality of choice for detecting the underlying source of infection, if it can be afforded and the patient is fit enough to be transported.

Effective treatment of zygomycosis requires early diagnosis and surgical drainage of the abscess. Unlike pyogenic brain abscesses, those caused by zygomycosis produce less prominent intraparenchymal abscess cavities. Instead, cerebritis and granulomatous inflammation with pus collection in the sulci are frequently seen, as in this case (Fig b). This explains why surgical drainage may not be as effective for this type as it is for pyogenic brain abscesses. In this regard, the most important treatment for zygomycosis is an antifungal agent able to penetrate the central nervous system (CNS) effectively. Amphotericin is the treatment of choice for CNS absidiomycosis. Typically, high-dose amphotericin, up to 1 to 1.5 mg/kg/day, is needed for this indication. Other antimycotic drugs such as 5-flucytosine, caspofungin, voriconazole, and itraconazole are not recommended, as they have limited activity against Zygomycetes such as *Mucor*, *Rhizopus*, and *Absidia*.^{7,8} In most cases,

zygomycosis carries a poor prognosis. The mortality rate varies between 30 and 70% in the rhinocerebral form whereas disseminated zygomycosis has a mortality rate of up to 90%. Possible complications of zygomycosis include the partial loss of neurological function, blindness, and thrombosis of the cerebral and pulmonary circulations.

In patients who do not respond to standard amphotericin, the administration of liposomal amphotericin (3-10 mg/kg/day) should be considered because this makes it possible to use higher doses with less toxicity. This preparation was not registered locally for clinical use at the time we managed this patient (2003). His lack of response to intravenous antimycotic agents and surgical drainage led us to decide to manage him with intraventricular amphotericin. This unusual form of antifungal treatment has been reported in adult neurosurgical patients with cerebral coccidioidal meningitis and mucormycosis.⁹⁻¹² Potential side-effects of intraventricular administration of amphotericin B include headache, vomiting, arachnoiditis, cranial nerve palsies, and paraparesis. These risks must be weighed against the inevitably fatal outcome of

inadequately treated rhizomycosis and the treatment should be performed under meticulous monitoring. In our patient, the rapid improvement of his conscious state and normalisation of CRP level after several doses of intraventricular amphotericin support its efficacy as a means of treating rhizomycosis.

There are no widely accepted guidelines on the duration of antifungal treatment for CNS fungal infections. Antifungal chemotherapy is usually recommended until all clinical, laboratory, and radiographic abnormalities have resolved (ie at least 4-6 weeks). In our patient, intravenous and intraventricular amphotericin was given for a total of 3 months, by which time the radiological and laboratory abnormalities had returned to normal.

In conclusion, we report a case of *Absidia* brain abscess in an immunocompetent 3-year-old boy who presented initially with severe acute gastroenteritis. A high index of suspicion followed by timely histological and microbiological investigations is needed to diagnose absidiomycosis, which can occur even in patients with no underlying immunodeficiencies. Intraventricular amphotericin is a useful adjuvant antifungal treatment for CNS zygomycosis.

References

1. Krauze A, Krenke K, Matysiak M, Kulus M. Fatal course of pulmonary *Absidia* sp. infection in a 4-year-old girl undergoing treatment for acute lymphoblastic leukemia. *J Pediatr Hematol Oncol* 2005;27:386-8.
2. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev* 2000;13:236-301.
3. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005;41:634-53.
4. Constantinides J, Misra A, Nassab R, Wilson Y. *Absidia corymbifera* fungal infection in burns: a case report and review of the literature. *J Burn Care Res* 2008;29:416-9.
5. Balasubramanian VP. Successful treatment of *Absidia corymbifera* brain abscess in a lung transplant recipient: a case report. *Chest* 2006;130(Suppl):296S-297S.
6. Drug used by patients in cases of mucormycosis found contaminated. Department of Health website: <http://www.dh.gov.hk/textonly/english/press/2009/090306-2.html>. Accessed 28 Mar 2009.
7. Black KE, Baden LR. Fungal infections of the CNS: treatment strategies for the immunocompromised patient. *CNS Drugs* 2007;21:293-318.
8. Mattiuzzi G, Giles FJ. Management of intracranial fungal infections in patients with haematological malignancies. *Br J Haematol* 2005;131:287-300.
9. Hamilton JF, Bartkowski HB, Rock JP. Management of CNS mucormycosis in the pediatric patient. *Pediatr Neurosurg* 2003;38:212-5.
10. Stevens DA, Shatsky SA. Intrathecal amphotericin in the management of coccidioidal meningitis. *Semin Respir Infect* 2001;16:263-9.
11. Winn WA. The treatment of coccidioidal meningitis. The use of amphotericin B in a group of 25 patients. *Calif Med* 1964;101:78-89.
12. Young RF, Gade G, Grinnell V. Surgical treatment for fungal infections in the central nervous system. *J Neurosurg* 1985;63:371-81.