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Fungal brain abscess: report of three cases and review of literature

Shahindokht Bassiri–Jahromi^{1*}, Kamyar Iravani²

¹Medical Mycology Department, Pasteur Institute of Iran, Tehran, Iran ²Otolaryngology Department, Shiraz University of Medical Science, Shiraz, Iran

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1. Introduction

Fungal intracranial abscess (usually referred to as brain abscess) is a complication of immunosuppression and is a rare pathologic condition in immunocompetent patients, which generally affects immunosuppressed patients^[1].

Fungal brain abscess has a high incidence of morbidity and mortality caused by several factors and therefore requires accurate diagnosis and appropriate medical management strategies to optimize the outcome^[2,3]. This increase in frequency is attributed to the growing use of immunosuppressive therapies and organ transplantation^[4–6]. The causative agents of fungal

Tel: +989122972237

Fax: +98664964435

E-mail: basiri@pasteur.ac.ir

ABSTRACT

Fungal brain abscess is an unusual but serious complication associated with immunosuppression. The aim of this study is to review our experience, to determine the factors related to the outcome, the pathogenesis and clinical presentation, and to improve the therapeutic strategy for this disease, and also include a review of the relevant literature.

We reviewed three cases of fungal brain abscess in patients who were immunocompromised. The three patients included two males and one female. Their ages ranged from 35 to 53 years (mean, 43.3 years). The mean duration of symptoms before diagnosis of brain abscess was 19 days. The diagnostic of brain abscess were performed in all three cases by histopathology and direct preparation, culture techniques and CT scan or magnetic resonance imaging. Patients were presenting with mild dizziness and unsteady gait, headache, and focal or generalized seizure.

We isolated two cases of *Aspergillus fumigatus* and one *Candida albicans* from cerebral abscess. All patients had predisposing factor to fungal infections. The outcome in our patients was poor, with an overall mortality of 2:3 of patients. Blood and urine culture were negative for fungi in all patients. Early diagnosis, aggressive surgical procedures, and antimicrobial therapy for fungal brain abscess may reduce morbidity and mortality.

brain abscesses in immunocompromised patients are Aspergillus species, Candida species, and rare fungi, including Cladophialophora bantiana and Cladosporium trichoides, Pseudallescheria boydii, Trichoderma species, Chaetomium species, Penicillium marneffei, and the Phaeohyphomycosis^[7].

The present study describes the clinical characteristic, and the fungi involved in the patients with brain fungal abscess and therapeutic factors inducing the outcome of brain abscess and improves the treatment strategy by reviewing the cases diagnosed at our institution and also is a review of the relevant literature.

2. Patients and methods

In a retrospective study, three patients with brain abscess entered the study. Predisposing factors were seen

^{*}Corresponding author: Shahindokht Bassiri-Jahromi, Medical Mycology Department, Pasteur Institute of Iran, Tehran, Iran.

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in all patients. The material for investigations was biopsy specimens from brain abscesses. Diagnosis was established on histopathology, direct preparation and microbiological studies including culture of brain abscess material, CT, and/or magnetic resonance imaging (MRI). Specimens were cultured on Sabouraud dextrose agar, blood agar and brain heart infusion agar, and fluid thioglycolate, anaerobic culture media, and biochemical properties. Duplicate cultures on each medium were incubated at 35 °C and 25 °C regularly, examined up to 4 weeks and identified using standard methods.

Only mass-forming lesions with pathologically proven fungal involvement were included; infections without related mass-forming lesions and abscesses were excluded from this study.

This study was approved by the Ethics Committee of Pasteur Institute of Iran and it conformed to the provisions of the Declaration of Helsinki. All patients were fully informed of the study protocol and gave an informed consent prior to study entrance.

3. Case report

3.1. Case 1

A 35-year-old Iraqi refugee woman was diagnosed with acute lymphatic leukemia (ALL). She was hospitalized in the infection disease section because of fever (38.5 °C) with disturbance and complaining of weakness of the left arm and the left leg, with 5 days of headache, nasal discharge and decreased visual acuity. The neurological examination revealed bilateral papilledema, bitemporal hemianopsia and impairment of visual acuity. MRI of the brain revealed a 2.5- cm multilobular abscess.

Direct microscopic and histopathological examination from brain abscess specimen showed hyaline, branched and septate hyphae compatible with fungal elements (Figure 1). Cultures of the brain abscess specimen grew *Aspergillus fumigatus* (*A. fumigatus*). Although antifungal treatment was started by amphotericin B (1.2 mg/kg/day) with fluconazole (400 mg/day), the patient was poor response to treatment and the patient's condition continued to deteriorate. MRI at that time did not demonstrate any improvement. The patient remained neurologically stable. Finally, the patient died 5 days after the surgery.



Figure 1. Hematoxilin and eosin stain of biopsy specimen of brain, highlighting *Aspergillus* sp. hyphae in the brain.

3.2. Case 2

The patient was 53-year-old man with a 3 years' history of tuberculosis, which was indicated by brucellosis for 2 months. He was treated by acyclovir metronidazole, rifampin, isoniazid, and trizianamid. He had refractory intense headache. Seven days before admission, he presented with painful ophthalmoplegia, ptosis, visual impairments, and occlusion. He had headache, vomiting, generalized tonoclonic seizures, fever, confusion, and altered sensory.

Directly biopsy specimen of brain microabscesses with 10% potassium hydroxide and Gram stain showed the presence of pseudomycelium and yeast cells. Culture of specimen gave rise to *Candida albicans* (*C. albicans*). It was identified by API 20 C Aux. After the operation, amphotericin B, and fluconazole therapy were started. During a 6-month follow-up period, the patient's headache and nasal discharge disappeared, and his visual acuity improved. The patient was maintained on the antifungal medication until complete radiographic resolution occured.

3.3. Case 3

A 42-year-old man suffered from chronic sinusitis and a progressive severe headache for a period of over one year. He has been employed as a structure worker for several years. CT scans showed paranasal sinusitis. He was presented with a history of cerebral concussion followed car crushed when he was 14-year-old. His CT scan revealed two lesions in the anterior and basal parts of the right temporal lobe. He had neck stiffness, without any fever, vomiting, Todd's palsy or double vision. Direct examination of cerebral tissue with 10% potassium hydroxide and histopathological examination of the brain abscess specimen showed the presence of septate hyphae (Figure 2). The brain abscess specimen cultures were positive for *A. fumigatus* (Figure 3). The patient was initially started on liposomal amphotericin B 450 mg (5 mg/kg) intravenously per day and oral voriconazole (400 mg/day). Unfortunately, despite antifungal therapies, the prognosis continued to be very poor in the patient and he died after 3 days.



Figure 2. Gomori methenamine silver stain of cerebellar tissue showing fungal elements.



Figure 3. Microscopic morphology of *A. fumigatus* isolate of brain abscess, stained with lactophenol cotton blue.

4. Discussion

Cerebral fungal abscess may occur in both immunocompetent and immunocompromised patients and is illustrated as an acute or chronic course. The mortality rate for fungal brain abscesses in immunosuppressed patients remains high[6].

In the present study, the predominant fungal brain abscess demonstrated by histopathology and tissue culture was *A*. *fumigatus* (2/3), followed by *C*. *albicans* (one case). Although various fungi have been described as agents of brain abscess mycosis, most fungal brain abscesses can be caused by yeast and *Aspergillus* sp. Fungal brain abscesses are associated with immunocompromised status, and poorly controlled diabetes in the infection by zygomycetes^[8,9]. The central nervous system is the most common secondary site of invasive disease after the lung that is the most common site of primary infection^[10].

The most prevalent fungal etiologic agents of brain abscess in patients undergoing marrow transplantation at the Fred Hutchinson Cancer Research Center in Seattle were Aspergillus species (58% of cases), and Candida species were second in frequency (33%); sporadic cases were caused by Rhizopus, Absidia, Scopulariopsis, and Pseudallescheria species^[10-12]. In present study, all three patients presented with known predisposing factors including ALL in the first case, tuberculosis accompanied with brucellosis in the second case, and chronic sinusitis after a concussion following a car accident in childhood and head fraction in the third case. In our study, the mortality rate of immunocompromised patients with aspergillosis brain abscess was quite high. The cases with Aspergillus abscesses had a fatal outcome^[7]. Unfortunately, despite aggressive surgical and antifungal therapies, the prognosis continued to be very poor in the patients with aspergillosis and the two patients with brain aspergillosis died.

Fungal brain abscess is associated with a very poor prognosis and high mortality. Despite antifungal therapy, the mortality in intracranial aspergillosis remains high^[13]. Walsh *et al.* reported that only 1 of 17 patients with this condition was successfully treated^[14]. Therefore, an early and precise diagnosis may prove to be life–saving in patients with the diagnosis of brain abscess^[15]. The accurate diagnosis of this rare disease can only be established by histopathological examination of tissue obtained at surgery. The clinical and laboratory diagnosis of cerebral aspergillosis (CA) is challenging and even in cases receiving appropriate treatment, mortality is very high.

The management of cerebral fungal abscesses is controversial. The optimal treatment is surgical resection combined with antifungal therapy preferably with voriconazole, which has made good prognosis in most cases of fungal brain abscess^[16].

The immunosuppression is a risk factor for fungal brain abscess^[17]. As seen in our study, ALL was present and may

In the second case, the patient was treated for tuberculosis with antituberculous agents and steroids for various periods, which could have impaired host immune response.

In the third case, the patient had evidenced of a paranasal sinus involvement. There were occupation factor (structure worker), cerebral concussion and chronic sinusitis as disposing factors. A hot, dry climate and a high content of *Aspergillus* spores in an atmosphere full of dust where he works may be responsible for its infection. Fungal brain abscess is specifically soil–associated occupations such as mining^[18].

The infection originates in the palate or paranasal sinuses and spreads through the orbit and adjacent sinuses into the brain. The way of infection from *Aspergillus* has been described as via hematogenous means, direct extension, or as a primary intracranial lesion^[19].

Table 1 indicates some cases reported fungal brain abscess with respect to age, sex and predisposing factor, date of survey publication and fungal isolate in patients with brain abscess. CA in the immunosuppressed patients, with haematological malignancies, progressed with a mortality rate of over 95%[20].

Clinical symptoms of CA are nonspecific, and an accurate diagnosis of this rare disease can only be established by tissue histopathology and positive biopsy culture^[15].

In our study, contiguous infections, hematogenous spread from other foci, and immunocompromised conditions were the most reason for aspergillosis and unfortunately both patients with *Aspergillus* brain abscess died.

In immunocompromised patients, when there is involvement of the central nervous system with *Aspergillus* infection, mortality may be as high as 95%. The clinical and

Table 1

Cases reported fungal brain abscess with respect to age, sex and predisposing factor, date of survey publication and fungal isolate in patients with brain abscess.

Author	Date and	Age and	Predisposing factor	Causative agents	Treatment	Outcome
	region of	sex				
	survey					
Yoo et al.[25]	1985/USA	54/M	Malignant lymphoma	Pseudallescheria boydii	Chemotherapy and/or radiotherapy	Failed
Loeys et al.[26]	1999/Belgium	5Y/M	Mucocutaneous candidiasis	C. albicans	Itraconazole and fuconazole	Cured
Endo <i>et al</i> .[27]	2001/Japan	55Y/M	transsphenoidal surgery for a pituitary adenoma	A. fumigatus	Amphotericin B and fluconazole	Failed
Lee <i>et al.</i> [28]	2003/Singapore	65Y/F	Cadaveric liver transplant for autoimmune hepatitis	Xylophypha bantiana	Amphotericin, itraconazole and	Cured
					flucytosine	
Singh et al.[29]	2004/India	20Y/M	Tuberculosis	Cladosporium bantianum	Amphotericin B and fluconazole	Cured
Lyons et al.[30]	2005/USA	64Y/M	Uncertain immune function	Cladophialophora bantiana	Amphotericin B and voriconazole	Cured
Roche et al.[31]	2005/Irland	26Y/M	X-linked isolated T-cell deficiency (probably Duncan's	Cladophialophora	Intravenous liposomal amphotericin B	Failed
			syndrome)	bantiana	and flucytosine	
Tsai <i>et al.</i> [10]	2006/Taiwan	48Y/F	Psoriasis for 20 years, treated with UV light, and cervical	Aspergillus species	Amphotericin B	Failed
			carcinoma			
Chakrabarti et	2006/India	14-M/M	Unknown	Aspergillus nidulans	Surgical drainage and amphotericin B	Failed
al.[32]						
Metellus et al.[33]	2008/France	42Y/F	Hepatitis C	Zygomycetes	Surgical endoscopic debridment and	Cured
					amphotericin B	
Garzoni et al.[4]	2008/	60 Y/F	Immunosuppressive therapies and organ transplantation	Cladophialophora	Posaconazole	Cured
	Switzerland			bantiana		
Iannotti et al.[34]	2009/USA	53Y/M	mixed aphas hypertension, benign prostatic hypertrophy,	Nocardia farcinica	Trimethoprim sulfamethoxazole,	Cured
			gastroesophaeal reflux, and hematuriaia		imipenem	
Liu et al.[35]	2010/China	65Y/F	Unknown	Aspergillus sp.	Voriconazole	Cured
Liu et al.[35]	2010/China	53Y/M	Unknown	Aspergillus sp.	Voriconazole	Cured
Liu et al.[35]	2010/China	56Y/F	Unknown	Aspergillus sp.	Voriconazole	Cured
Yampolsky et	2010/	51Y/M	Diabetes mellitus	C. albicans	Fluconazole, amphotericin B and	Cured
al.[23]	Argentina				radical surgery	
Turgut et al.[36]	2010/Turkey	22Y/F	Aplastic anemia	A. fumigatus	Liposomal amphotericin B and	Cured
					itraconazole	
McNeil et al.[37]	2011/USA	24Y/M	Chronic granulomatous disease	Phaeoacremonium	Voriconazole and trimethoprim	Cured
				parasiticum	sulfamethoxazole	
Chen <i>et al.</i> [38]	2011/China	46Y/F	Unknown	A. fumigatus	Voriconazole	Cured
Tammer et al.[12]	2011/Germany	31/F	AIDS	Scedosporium and	Caspofungin	Cured
				Pseudallescheria sp.		
Hoenigl et al.[9]	2013/Austria	59/M	Diabetes mellitus	Schizophyllum commune	Posaconazole	Cured
Present study	Iran	42/M	chronic sinusitis and history of cerebral concussion	Aspergillus flavus	Liposomal amphotericin B,	Failed
			followed car crushed		itraconazole and voriconazole	
Present study	Iran	35/F	ALL	A. fumigatus	Amphotericin B and fluconazole	Failed
Present study	Iran	53/M	Tuberculosis and brucellosis	C. albicans	Amphotericin B and fluconazole	Cured

laboratory diagnosis of CA is problematic and mortality is quite high, even in cases receiving appropriate treatment. Therefore, an early and accurate diagnosis may prove to be life–saving in patients with the diagnosis of CA^[15].

Candida meningitis can occur spontaneously as a complication of disseminated candidiasis or as a complication of an infected wound or direct inoculation of the organism into the central nervous system. The majority of brain abscesses due to Candida species are associated with other infections including the lungs, heart, spleen, kidneys and liver. Few surviving patients with intracranial infection due to *Candida* have been reported^[21]. Fungal brain abscess caused by *Candida* spp. is a rare disease, a nonspecific presentation, with few data on treatment, and generally poor outcomes. Diagnosis requires to be highly accurate, as clinical presentations and laboratory data can be nonspecific and difficult to diagnosis of bacterial brain abscesses. The mortality rate of the non-autopsy cases reviewed by Fennelly et al. was 69%[22]. The patient reported in this paper received amphotericin B with intravenous fluconazole. Treatment with amphotericin B and fluconazole, led to a favorable outcome. In patients with Candida brain abscess, radical excision and prolonged antifungal therapy based on fluconazole or amphotericin B are necessary to improve the prognosis of this type of patients^[23].

In vivo study has shown that voriconazole has high penetration into brain tissue and cerebrospinal fluid, with steady-state drug levels in the central nervous system twice those of plasma levels, and limited human data have suggested favorable pharmacokinetics^[24].

Outcome of *Aspergillus* brain abscesses is poor. The present study illustrated that outcome of brain abscesses due to *C. albicans* was better than *Aspergillus* sp. Brain aspergillosis is often rapidly fatal, even with surgical intervention. In the current study, both patients with *Aspergillus* brain abscess died.

5. Conclusion

Understanding the pathogenesis of brain abscesses is important in determining the causative microorganisms and treatment. Although outcome is frequently fatal in patients with fungal brain abscess, delay in the diagnosis also contributes to the high mortality.

Early diagnosis, aggressive surgical procedures, and

antibiotic therapy for fungal brain abscess may reduce morbidity and mortality.

Conflict of interest statement

We declare that we have no conflict of interest.

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