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Multiple intracranial abscesses due to *Cryptococcus neoformans*: an unusual clinical feature in an immunocompetent patient and a short review of reported cases

O. TORE*, S. AKCAGLAR*, E. KAZAK*, Y. HEPER*, H. AKALIN*, B. HAKYEMEZ†, B. ENER*, T. BOEKHOUT‡§ & F. HAGEN‡§

**Department of Microbiology and Infectious Diseases, †Department of Radiology, Uludag University School of Medicine, Bursa, Turkey, ‡CBS Fungal Biodiversity Center, Department of Yeast and Basidiomycete Research, Utrecht, The Netherlands, and §Division of Acute Medicine and Infectious Diseases, University Medical Centre Utrecht, Eijkman-Winkler Centre for Medical Microbiology, Infectious Diseases and Inflammation, Utrecht, The Netherlands*

We present a case of multiple intracranial abscesses caused by *Cryptococcus neoformans* in a patient who presented with no symptoms of immunodeficiency.

Keywords multiple intracranial abscesses, *Cryptococcus neoformans*, review of reported cases

Introduction

Cryptococcus neoformans is a yeast-like encapsulated fungus that is found worldwide in soil contaminated with bird excrement, particularly pigeon droppings [1]. Humans become infected by inhaling the organism and may remain asymptomatic with infection limited to the lungs. When limited to the lungs in immunocompetent hosts, *C. neoformans* infection may cause pneumonia, poorly defined mass lesions, pulmonary nodules, and, rarely, pleural effusion [2]. In immunocompromised hosts in whom there has been hematogenous dissemination, the fungus spreads primarily to the central nervous system (CNS), resulting in meningitis or sometimes intracranial abscesses or cryptococcoma but may also affect other organs [3]. Cryptococcosis can be fatal in patients who have impaired cell-mediated immunity caused by human immunodeficiency virus (HIV) infection, malignancy, diabetes mellitus (DM), or corticosteroid treatment [4]. Cryptococcosis is one of the most common fungal infections affecting the CNS, and most patients present with signs of meningitis and encephalitis [5]. We provide a case of multiple cryptococcal abscesses in an immunocompetent patient.

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Correspondence: O. Tore, Uludag University School of Medicine Department of Microbiology and Infectious Diseases, Bursa, Turkey. E-mail: okant@uludag.edu.tr

Case report

The patient was a previously healthy 54-year-old woman who presented with complaints of snoring and smelling unpleasant odors of five months duration and headaches, along with hearing buzzing sounds for two months. She was lethargic and had superior oblique paralysis of the right eye. Cranial magnetic resonance imaging (MRI) examination revealed cystic lesions in the posterior segment of the left internal capsule at the level of the left basal ganglia and a second cystic lesion extending subependimally along the occipital horn of the left lateral ventricle. There was no contrast enhancement around these lesions, but there was widespread edema in the white matter of the temporo-parietal region and mass effect with compression of the left lateral ventricle. Due to the edema, midline shifting to the right was observed, as well as a 1.5 cm-sized ring-enhancing lesion compressing mesencephalone at the level of the right ambient cysterna (Fig. 1).

The stereotactic biopsy from the lesion in the left occipital region did not provide sufficient material for appropriate analysis. A second stereotactic biopsy was taken from the lesion near the mesencephalon. Examination of frozen sections established the diagnosis of an abscess, and a therapy course of ceftiaxon (2 g two times per day iv) and metronidazole (500 mg three times per day iv) was initiated immediately.

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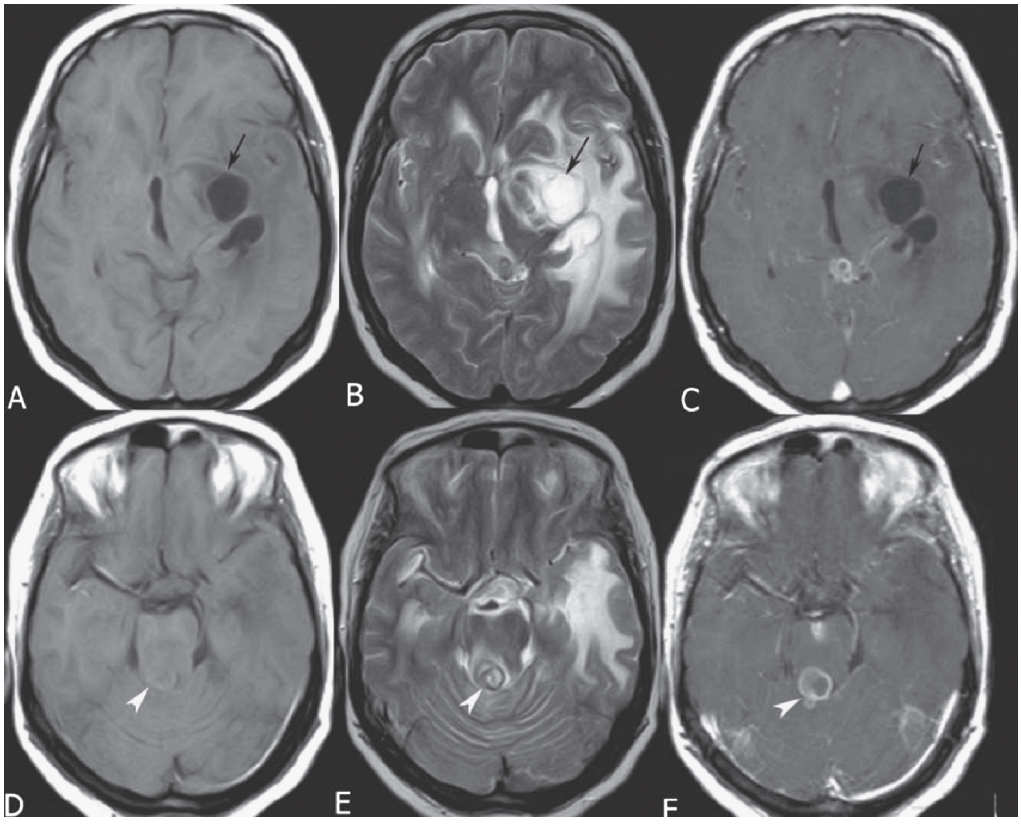

Fig. 1 *Cryptococcus neoformans* abscess in different regions of the brain. Interrelated cystic lesions (gelatinous pseudocyst) can be seen in the left basal ganglion. Lesions have prominent surrounding edema but did not enhance after contrast administration (A–C) (long arrows). A distinct ring-enhancing lesion with minimal mass effect is visible, located between the aquaductus Sylvii and the fourth ventricle. It is more heterogeneous than the others and has a thick capsule (D–F) (arrowhead).

After isolating *Cryptococcus neoformans* from the second biopsy material, the therapy protocol was changed to amphotericin B (1 mg/kg per day) and flucytosine (100 mg/kg per day). Due to problems in providing flucytosine, amphotericin B was continued as the sole antifungal. At day 3, an extraventricular drainage system (EVDS) was introduced by neurosurgeons to drain cerebrospinal fluid (CSF) which resulted in the drainage of 5 cc of CSF every 3 h. Examination of the ventricular CSF showed 170 mm^{-3} white blood cell (granulocyte predominance), 5,000,000 mm^{-3} red blood cell, and 41 mg dl-1 glucose.

Serum tests for HIV antibodies were twice negative and her serum glucose values were between normal levels. There was no history of direct contact with pigeons or bird droppings. Examinations of her immune status showed no pathological properties (IgA: 216 mg dl^{-1}; IgM: 123 mg dl^{-1}; Ig G: 1310 mg dl^{-1}; C3c: 146 mg dl^{-1}; C4:26.7 mg dl^{-1}; NBT: 100%; IgG subgroups were normal limits; only the ratio of CD4/CD8: 0.92). Due to a tonic-clonic seizure attack, an anti-epileptic drug (Epdantione, tab 3 × 100 mg) was added to the therapy. At day 11, CSF examination showed 90 mm^{-3} WBC, and direct microscopic examination revealed budding yeasts but neither yeasts nor bacterial were recovered in culture. Due to renal failure, treatment was changed to liposomal amphotericin B 5 mg/kg/d. At day 17, the EVDS was withdrawn, and therapy continued with fluconazole (400 mg two times per day iv).

Repeated cranial MRI showed that cystic lesions, which extended subependimally at the level of the left temporal and parietal lobes, decreased in size. But there were no significant differences in the size of lesions at the level of the aquaductus Sylvii. Because of edema around the lesions, the left ventricle was compressed, and some images indicated evidence of hydrocephalus. The patient displayed substantial regression in her neurological status, in that she experienced neck stiffness, spoke unconsciously, had memory loss, and failed to recognize her relatives. Due to vomiting after feeding, mannitol was added to her therapy to suppress regurgitation. There was no electrolyte imbalance.

At day 25, due to high fever and pyuria, Cefepim (1 g two times per day iv) was added but was later changed to Meropenem (1 g three times per day iv), according to the

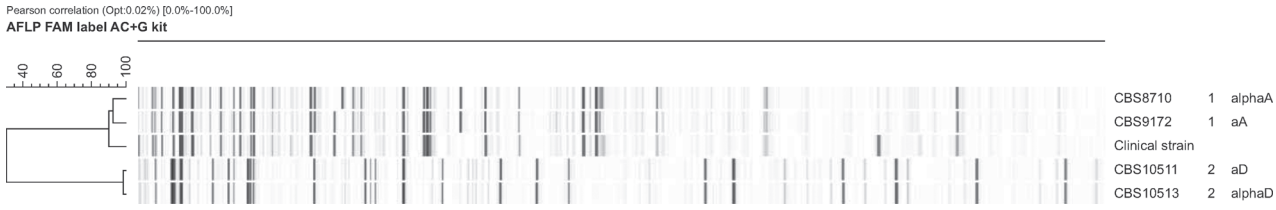

Fig. 2 AFLP genotyping of original and control strains. Amplified Fragment Length Polymorphisms (AFLP) fingerprint analysis (Boekhout *et al*., 2001 [6]) of the *Cryptococcus* strain cultured from the patient described in this report (clinical strain) including two reference strains from each serotype of *Cryptococcus neoformans* (CBS8710 and CBS9172 = *Cryptococcus neoformans* variety *grubii*; CBS10511 and CBS10513 = *Cryptococcus neoformans* variety *neoformans*).

antibiogram of a positive urine culture. Her high fever regressed, but at day 38 she experienced another fever attack. Teicoplanin (400 mg two times per day iv) was then added to her therapy and maintained at 400 mg per day iv. At day 39, her condition worsened, and on the 40th day after the start of treatment she died.

Mycological studies

Five days after the inoculation of biopsy samples on Sabouraud dextrose agar, cream-colored mucoid colonies were noted. Microscopic studies of Gram-stained and India ink preparations of portions of the colonies revealed encapsulated yeasts cells. Germ tube tests were negative, there was no hyphal growth on cornmeal agar, urease test was positive, and colonies grew at 25°C and 37°C. The isolate from the brain abscess was identified as *Cryptococcus neoformans* using API 20C AUX (BioMerioux SA, Marcy-l'Etoile/FRANCE) and by the Rapid Yeast Plus Identification System (REMEL Inc., Lenera, KS/USA). The *Cryptococcus* isolate was further typed using a serotype agglutination test (F. Dromer, Pasteur Institute, Paris, France) and genotyped by Amplified Fragment Length Polymorphism (AFLP) fingerprint analysis, as described by Boekhout *et al.* [6].

Discussion

It is often difficult to reach a definitive diagnosis in cases of cryptococcal CNS infection. The clinical presentation and the findings from routine hematological, biochemical and CSF tests can overlap with those of a variety of non-infectious and infectious etiologies [2–5].

When immunocompromised patients develop cryptococcal CNS infections, the clinical picture is nearly always severe, and most patients present with signs of meningitis and encephalitis [5]. Cryptococcoma and brain abscess is a rare entity, characterized by solid tumor-like masses usually found in the cerebral hemispheres or the cerebellum or more rarely in the spinal cord [7,8]. Cryptococcal brain abscesses are often solitary, but in some instances they may be multiple. Five cases of multiple cryptococcal brain abscesses have been described to date in the literature [9–13]. Clinical properties of these cases were summarized in Table 1. Although HIV infection is very rare in Turkey, the number of cases of acquired immunodeficiency syndrome (AIDS) is still rising, and cryptococcal brain abscesses may occur in patients with AIDS or other immunocompromising disorders. Immunocompetent patients must also be assessed carefully in order to avoid delayed diagnosis [14]. The prognosis is better for HIV-associated cases of cryptococcal CNS infection, including meningitis, than in non-HIV patients. In a 1992–2000 population-based surveillance study, 21% of patients with non-HIV-associated cryptococcosis died during their first hospital admission or within 30 days after their first discharge (i.e., while receiving outpatient care). The corresponding figure for HIV-associated cases was 11%, with most of these deaths occurring within the first several weeks of CNS involvement [15]. Delayed diagnosis is an

Table 1 Summary of cryptococcal brain abscess cases

Reference	Age, sex	Underlying disease and concurrent infection	Culture samples	Treatment outcome	Infection
Riccio TJ, *et al.* [9]	NA	NA	NA	NA	NA
Huang JL, *et al.* [10]	17, F	SLE, meningitis and pulmonary infection	Blood and brain abscess	Amp-B, 5-flu, Fluc	Resolved
Wang JH, *et al.* [11]	30, M	HIV	Blood and brain abscess	Amp-B, Fluc	Died
Saigal G, *et al.* [12]	49, M	None	CSF	Amp-B, 5-lu, Fluc	Improved
Athanassiadou F, *et al.* [13]	5, M	B-ALL	Urine + PCR + Cry-Ag	Lam-B, ceftazidime	Died

NA, not available; M, male; F, female; SLE, systemic lupus erythematosus; B-ALL, B cell acute lymphoblastic leukemia; Cry-Ag, cryptococcus antigen;Amp-B, Amphotericin-B; 5-flu, 5-flucytosine; Fluc, fluconasole; Lam-B, liposomal amphotericin-B.

important issue in the treatment of cryptococcosis. Shih *et al*. [16] reported a crude mortality rate of 19.1% (18 deaths) in 94 cases of non-HIV-associated cryptococcal meningitis. Seven of these patients died before anti-fungal treatment was even administered and all were cases of delayed diagnosis. To avoid this situation, radiological imaging studies must be performed, and the patient should be evaluated according to radiological findings for stereotactic biopsy. In our case, the diagnosis of brain abscess was determined on the basis of MR findings (Fig. 1), and antibacterial therapy was immediately initiated. After the isolation of *C. neoformans* from the abscess material, obtained by the second stereotactic biopsy, treatment was changed to amphotericin B and at day 17 switched to fluconazole.

Several randomized controlled trials in patients with AIDS-related cryptococcal meningitis have shown excellent results when induction therapy is administered in the form of amphotericin B combined with flucytosine, followed by consolidation therapy with fluconazole [17]. The recommended treatment in the absence of HIV is the same for both cryptococcal CNS infection and meningitis patients, although no controlled trials have been conducted comparing the azoles with amphotericin B in this population [18]. Research has also indicated that high-dose fluconazole treatment is an effective and safe initial treatment for cryptococcal meningitis in patients with AIDS [19].

In conclusion, although uncommon, *C. neoformans* infection should always be considered in cases of meningitis, meningoencephalitis, or brain abscesses that occur in patients with immunocompromising conditions other than AIDS, as well as in immunocompetent patients. As was observed in this case, if there are ring-enhancing lesions in MR studies, cryptococcosis must be considered, as well as other etiologic agents, and detailed studies must be performed to identify the causative organism [13,19]. To ensure accurate and definitive diagnosis, if stained or unstained yeast or yeast-like cells are observed on direct microscopic examination of clinical material, the material should be centrifuged and an India ink preparation should always be prepared for analysis. Furthermore, this case indicates that it can take 5–6 days before fungal growth appears on culture media in cryptococcal infections. This suggests that microbiologic cultures must be incubated longer than usual in this patient group.

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