*Cryptococcus albidus* encephalitis in newly diagnosed HIV-patient and literature review

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**Abstract**

We present the first case of encephalitis caused by *Cryptococcus albidus* due to AIDS. In addition, we give an overview of the literature of extra-dermal infection cases caused by *C. albidus*. In the 21 cases, HIV and organ transplantation were important risk factors especially in recent 20 years. Fungal culture or India ink preparations are the best way to demonstrate *C. albidus* in both serum and CSF.

**1. Introduction**

Cryptococcus infection is relatively uncommon, except among immunocompromised individuals. The most common human pathogenic species is *Cryptococcus neoformans*. However, more and more opportunistic infections associated with non-neoformans cryptococcus have been reported. *Cryptococcus albidus* has recently been reported to be a rare cause of infection in humans. There are only 6 cases reported *C. albidus* as a cause of intracranial infection [1]. Here we report another case of cryptococcus encephalitis caused by *C. albidus* who was the first case *C. albidus* encephalitis in an HIV patient. We also reviewed the literatures on risk factors, diagnosis and treatment of *C. albidus* extra-dermal infection in humans.

**2. Case**

A 28-year-old heterosexual male attended emergency department and was preliminary diagnosed as encephalitis in April 6th 2013(day 0), then he was admitted to Intensive Care Unit of a teaching hospital. The patient complained diplopia, vomiting, tinnitus, vertigo and tumbling 3 times from day-3. He denied any family history and medical history except having a cold 2 weeks ago. The patient presented with neck stiffness, strabism and discontinuous confusion. He denied fever, headache and denied taking any medication. Physical examination revealed his left thorax signs of crusting herpes zoster.

When the patient was admitted, he was fully conscious and his urinary amount was about 100 ml/h. His blood pressure was 105/60 mmHg and pulse 115 /min, Body temperature 36.8 °C. At day 0, laboratory data revealed a white blood cell count of 6.69 × 10⁹ /l (84.0% neutrophils, 6.6% lymphocytes and 9.3% monocytes), hemoglobin level of 12.1 g/dl, platelet count 142 × 10⁹ /l and the count of CD4 positive white blood cell was 7.1 cells/μl and CD8 positive was 150.5 cells/μl, and normal urinalysis, liver function tests, chest radiograph and head computed tomography (CT).

The patient had signs of meningeal involvement and a lumbar puncture was performed 2 h after admitted. The pressure for the lumbar puncture was 32 cm H₂O; cerebrospinal fluid (CSF) was clear with 8 white blood cells/μl and no red cell was found. CSF protein was 272 mg/dl (normal reference: 150–450 mg/dl) and glucose was 1.11 mmol/l (normal reference: 2.2–3.9 mmol/l). India ink staining revealed the presence of encapsulated yeast. Eight hours after admitted to hospital, the patient developed seizures and sank into a coma. Soon the patient appeared hypotension, abnormal breathing rhythm and was given tracheal intubation and mechanical ventilation. At day 1, he was reported HIV antibody positive.

After the patient admitted, he was administered with Ceftriaxone and Aciclovir. As India ink staining revealed the presence of encapsulated yeast, considering amphotericin B was unavailable in time, intravenous fluconazole therapy was immediately started. He died at day 3 due to cureless low blood pressure.
At day 5 (2 days after patient's death), Culture of the CSF showed growth of *C. albidus*.

3. Discussion

Cryptococcus infection is relatively uncommon, except among immunocompromised individuals. The most common human pathogenic species is *C. neoformans*. However, more and more opportunistic infections associated with non-neoformans cryptococcus have been reported. *C. albidus* has recently been reported to be a rare cause of infection in humans. There are only 20 reported cases of extra-dermal infection to date (see Table 1) [2–16]; most of cases were reported *C. albidus* as a cause of bacteremia in humans and only 6 cases as a cause of intracranial infection. Here we report another case of cryptococcus encephalitis caused by *C. albidus* who was the first case *C. albidus* encephalitis in an HIV patient. We also reviewed the literatures on risk factors, diagnosis and treatment of *C. albidus* infection in humans.

There are seven commonly recognized species of Cryptococcus. *Neoformans* cryptococcus is the most common human pathogenic species and non- *neoformans* cryptococcus have rarely reported as human pathogens. *C. albidus* is very similar to *C. neoformans* in morphology, but can be differentiated because it is phenol oxidase negative, and when grown on birdseed agar *C. neoformans* produces melanin causing the cells to take on a brown color while the *C. albidus* cells stay cream colored.

We report here a case of *C. albidus* encephalitis, based on available diagnostic methods, in a HIV-infected patient and review relevant literature on this infection. A comprehensive review of the literature was performed on case reports of infection due to *C. albidus* in patients in Medline from its inception until July 2013. Search terms employing the key words: fungus, infection, meningitis, encephalitis, Cryptococcus, non- *neoformans*, albidus. References in each manuscript were reviewed to identify additional cases of *C. albidus* infections.

*C. albidus* is a rare non- *neoformans* Cryptococcus that has been associated with human infections. Including our case, there have

### Table 1

| Year of case published [reference] | Age | Sex | Risk factor(s) | Infection site | Duration of symptoms | Treatment | Outcome |
|----------------------------------|-----|-----|----------------|----------------|----------------------|-----------|---------|
| 1965                             | 75  | M   | Psychiatric history, lung cancer on autopsy | Cerebrospinal fluid | 1 Month | None | Death |
| 1968                             | 73  | F   | Polycythemia vera | Cerebrospinal fluid | 5 Days | None | Death |
| 1970                             | 48  | M   | None; glioblastoma of the basal ganglia later developed | Cerebrospinal fluid | Unknown | None | Survived |
| 1970/1972 [2]                    | 68  | M   | Cigarette smoker, poor dentition | Lung | 6 Months | Amphotericin B (1.0 g) | Survived |
| 1971/1973 [3]                    | 45  | M   | Air conditioner repairman, exposure to pigeon excrement | Cerebrospinal fluid | 3 Days | Amphotericin B (1.5 g) | Survived |
| 1971                             | 20  | M   | Psychiatric illness, neurologic illness | Cerebrospinal fluid | > 20 Months | None | Survived |
| 1978/1980 [4]                    | 29  | M   | Mentally retarded, juvenile rheumatoid arthritis, corticosteroids, alcoholic liver disease, arteriovenous malformation of cerebellar artery | Cerebrospinal fluid | 36 Days after repair of arteriovenous malformation | Amphotericin B (unknown total dose) | Death 18 days into therapy |
| 1987/1987 [5]                    | 65  | F   | Acute myelogenous leukemia with severe neutropenia | Blood | 5 Days | Amphotericin B (235 mg), Flucytosine (150 mg/kg/day for 7 days) | Death 11 days into therapy |
| 1987/1989 [6]                    | 45  | M   | Pemphigus foliaceus, corticosteroids, cyclophosphamide | Blood | Unknown | Oral ketoconazole (unknown total dose) Amphotericin B (1.9 g) | Survived |
| 1989/1993 [7]                    | 37  | M   | End-stage renal disease, hemodialysis, coinfection with mucormycosis | Pleural fluid | 3 Weeks | Amphotericin B (1.9 g) | Survived |
| 1993                             | 40  | M   | AIDS, complicated by pneumocytis carinii infection | Blood | 2 Weeks | Oral fluconazole | Survived but died later due to recurrence |
| 1996/1998 [8]                    | 47  | F   | AIDS, complicated by CNS toxoplasmosis, MDS | Blood | 20 Days | Amphotericin B and flucytosine Flucytosine and itraconazole | Death 14 days into therapy Death: cardiorespiratory arrest Survived |
| 1996/1996 [9]                    | 38  | M   | AIDS, complicated by *Pneumocytis carinii* infection | Blood | 1 Month | Oral azithromycin and paromycin Amphotericin B and oral Itraconazole | Survived |
| 1998/1998 [10]                   | 4   | F   | Acute lymphocytic leukemia | Blood | Unknown | Oral azithromycin and paromycin | Survived |
| 2004/2004 [11]                   | 51  | M   | dependent diabetes; AML and chemotherapy; progenitor cell transplantation | Blood | 6 Weeks | Amphotericin B and oral Itraconazole | Survived |
| 2001/2004 [12]                   | 23  | M   | Renal transplantation | Disseminate: blood, skin, lung | 10 Days | Oral fluconazole | Survived |
| 2001/2004 [13]                   | 16  | F   | AIDS, inhale fluticasone due to asthma | Scleral ulceration Keratitis | 1 Week | Amphotericin B and Itraconazole | Resolved after 4 weeks therapy Healed |
| 2004/2005 [14]                   | 69  | F   | Corneal transplantation | Keratitis | 7 Months | Amphotericin B Remove the corneal button and repeat transplant | Survived |
| 2007/2013 [15]                   | 44  | M   | Immunosuppressive therapy because of Still's disease | Lung | 6 Months | Amphotericin B | Death after 10 days therapy Survived |
| 2012/2013 [16]                   | 55  | M   | Liver transplant | Blood | 34 Days | Posaconazole, remove central venous catheter Fluconazole | Death within 2 days |
been a total of 21 cases of \textit{C. albidus} extra-dermal infection in humans. Psychiatric history, chronic steroid exposure, organ transplantation, hematogenesis, AIDS are associated risk factors. With the increase in use of medical technology and devices, greater number of immunocompromised patients accompanies appeared and change the risk factors of \textit{C. albidus} infection. In the 11 cases reported in recent twenty years, all patients were concomitant with HIV/AIDS or organ transplantation patients except one with acute myeloid leukemia. So HIV/AIDS and transplantation become the main risk factors. Before our case, there were 6 \textit{C. albidus} intracranial infection cases, but all of those cases were reported before 1978 and the risks were neurologic disease (3 cases), mental disease (2 cases), hemopathoy (1 case) and exposure to pigeon excrement (1 case). Present case is the first \textit{C. albidus} intracranial infection due to AIDS.

\textit{C. albidus} infection has similar clinical manifestations as other cryptococcus infection. Cryptococcal encephalitis is one of the most important HIV-related opportunistic infections. Most patients with Cryptococcus encephalitis may absent the sign of fever, so did the patient in present case. Patients may show signs of meningeal irritation, cranial nerve palsies and focal neurologic abnormalities such as hemiparesis. CSF pressure may be normal or elevated, and the fluid is usually clear. Normal cell counts are common in immunosuppressed patients. CSF protein may be normal initially, subsequently rises, usually to levels not exceeding 200 mg/l. Glucose in normal or decreased but rarely below 10 mg/dl. Cryptococcal serum antigen assay is specific for the polysaccharide antigens found only on \textit{C. neoformans}. So a negative serum Cryptococcus assay does not rule out infection by species of Cryptococcus other than neoformans. Fungal culture or India ink preparations are the best way to demonstrate \textit{C. albidus} in both serum and CSF [17]. In present case, the patient showed meningeal irritation sign and cranial nerve injuries. CSF pressure elevated and India ink staining reveal the presence of encapsulated yeast and CSF culture show \textit{C. albidus} is the pathogen. Those all help to diagnosis of \textit{C. albidus} encephalitis. Patient show no fever probably result from the immunosuppression caused by AIDS.

The treatment for \textit{C. albidus} is not well defined. Amphotericin B has been modestly effective in the treatment of \textit{C. albidus}. \textit{C. albidus} encephalitis is considered had same therapy strategy as other cryptococcal encephalitis. A combination therapy of intravenous amphotericin B followed by fluconazole was recommended in treating cryptococcal encephalitis [18]. While in a recent randomized, controlled trial about therapy for cryptococcal encephalitis in patients with HIV infection, result suggested that compared with amphotericin B alone, treatment by amphotericin B plus fluconazole showed no survival benefit. Amphotericin B plus flucytosine was associated with improved survival and this was the most recommend treatment strategy [19].

In the 21 cases, 8 patients were died despite antifungal treatment were administered. Fifty seven percent (4 of 7 cases) \textit{C. albidus} encephalitis patients were died. Cryptococcal encephalitis is a significant cause of morbidity and mortality among persons with HIV/AIDS and mortality remains high. It is reported that more than 50% patient were died in a survey sub-Saharan Africa [20]. As the pathology of other cryptococcal encephalitis, main cause of death is brain stem compression. Even survival, patients often suffer optic atrophy, hydrocephalus, personality change and even dementia. This case emphasizes the importance of considering unusual emerging cryptococcal and suggests that \textit{C. albidus} should be added to the increasing number of causative agents of fungal infections in immunocompromised patients such as HIV infection.

**Conflict of interest**

There are none.

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**References**

[1] Khawcharoenporn T, Apisarnthanarak A, Mundy LM. Non-neoformans cryptococcal infections: a systematic review. Infection 2007;35(2):51–8.

[2] Krumholz RA. Pulmonary cryptococcosis. A case due to \textit{Cryptococcus albidus}. \textit{Am Rev Respir Dis} 1972;105(3):421–4.

[3] da Cunha T, Lusins J. \textit{Cryptococcus albidus} meningitis. \textit{South Med J} 1973;66(11):1230.

[4] Molto JC, Sinivasan S, Scott ML, Raff MJ. \textit{Cryptococcus albidus} meningitis. \textit{J Infect} 1980;2(1):79–82.

[5] Glauc CL, Myers JP, Pass LM. Cryptococcosis due to \textit{Cryptococcus albidus}. \textit{South Med J} 1987;80(4):511–3.

[6] Lin SR, Peng CF, Yang SA, Yu HS. Isolation of \textit{Cryptococcus albidus} var. albidus in patient with pemphigus foliaceus. \textit{Gaoxiong Yi Xue Ke Xue Za Zhi} 1989;3(2):126–8.

[7] Horowitz ID, Blumberg EA, Krevolin L. \textit{Cryptococcus albidus} and mucormycosis empyema in a patient receiving hemodialysis. \textit{South Med J} 1993;86(9):1070–2.

[8] Nordoadis T, Avlami A, Velagiakri A, Stefanou I, Georgakopoulos G, Papalambrouv C, et al. First report of \textit{Cryptococcus laurentii} meningitis and a fatal case of \textit{Cryptococcus albidus} cryptoccocemia in AIDS patients. \textit{Med Mycol} 1998;36(5):335–9.

[9] Loison J, Bouchara JP, Guebo E, de Gentile L, Cimon B, Chennebault JM, et al. First report of \textit{Cryptococcus albidus} septicaemia in an HIV patient. \textit{J Infect} 1996;33(2):139–40.

[10] Wells GM, Gajar A, Pearson TA, Hale KL, Shenep JL. Brief report. Pulmonary cryptococcosis and \textit{Cryptococcus albidus} fungemia in a child with acute lymphocytic leukemia. \textit{Med Pediatr Oncol} 1998;31(6):544–5.

[11] Ramachandren R, Gladstone DE. \textit{Cryptococcus albidus} infection in a patient undergoing autologous progenitor cell transplant. \textit{Transplantation} 2004;77(10):1556.

[12] Lee YA, Kim HJ, Lee TW, Kim MJ, Lee MH, Lee JH, et al. First report of \textit{Cryptococcus albidus}–induced disseminated cryptococcosis in a renal transplant patient. \textit{Korean J Intern Med} 2004;19(1):52–7.

[13] Garelick JM, Khodabakhsh AJ, Lopez Y, Ranji M, Lister M. Scleral ulceration due to \textit{Cryptococcus albidus} in a patient with pemphigus foliaceus. \textit{Gaoxiong Yi Xue Ke Xue Za Zhi} 1989;3(2):126–8.

[14] de Castro LE, Sarraf OA, Lally JM, Sandoval HP, Solomon KD, Vroman DT. \textit{Cryptococcus laurentii} fungemia due to \textit{Cryptococcus albidus} in a liver transplant recipient. \textit{QJM} 2003;96(9):637–40.

[15] de Castro LE, Sarraf OA, Lally JM, Sandoval HP, Solomon KD, Vroman DT. First report of \textit{Cryptococcus albidus} keratitis after corneal transplantation. \textit{Cornea} 2004;23(7):730–1.

[16] de Castro LE, Sarraf OA, Lally JM, Sandoval HP, Solomon KD, Vroman DT. First report of \textit{Cryptococcus albidus} keratitis after corneal transplantation. \textit{Cornea} 2004;23(7):882–3.

[17] Cleveland KO, Gelfand MS, Rao V, Posaconazole as successful treatment for fungemia due to \textit{Cryptococcus albidus} in a liver transplant recipient. \textit{J Infect} 2013;60(4):361–2.

[18] Burnik C, Atinias ND, Oizkaya G, Serter T, Selcuk ZT, Firat P, et al. Acute respiratory distress syndrome due to \textit{Cryptococcus albidus} pneumonia: case report and review of the literature. \textit{Med Mycol} 2007;45(5):469–73.

[19] Stamm AM, Poll SS. False-negative Cryptococcal antigen test. \textit{JAMA} 1988;244(12):1359.

[20] Perfect JR, Dismukes WE, Dromer F, Goldman DL, Hamill RJ, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. \textit{Clin Infect Dis} 2010;50(3):291–322.

[21] Day JN, Chau TT, Laloo DG. Combination antifungal therapy for cryptococcal meningitis. \textit{N Engl J Med} 2013;368(26):2522–3.

[22] Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. \textit{AIDS} 2009;23(4):525–30.