



Cryptococcus albidus encephalitis in newly diagnosed HIV-patient and literature review[☆]



Yang Liu, Shaolin Ma^{*}, Xuebin Wang, Wei Xu, Jin Tang

Intensive Care Unit, East Hospital, Tongji University School of Medicine, No. 150, Jimo Road, Pudong New Area, Shanghai 200120, China

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ABSTRACT

We present the first case of encephalitis caused by *Cryptococcus albidus* duo 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.

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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 6.69×10^9 /l (84.0% neutrophils, 6.6% lymphocytes and 9.3% monocytes), hemoglobin level of 12.1 g/dl, platelet count 142×10^9 /l and the count of CD4 positive white blood cell was 7.1 cells/ μ l and CD8 positive was 150.5 cells/ μ l, 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/ μ l 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 duo to cureless low blood pressure.

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^{*} Corresponding author. Tel.: +86 13310167499.

E-mail address: sehicu@gmail.com (S. Ma).

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
summary of date from cases of *Cryptococcus albidus* extra-dermal infection in humans

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)	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 pneumocystis 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	Death 14 days into therapy
1996/1996 [9]	38	M	AIDS, complicated by <i>Pneumocystis carinii</i> infection	Blood	1 Month	Fluconazole and itraconazole	Death: cardiorespiratory arrest
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	1 Week	Amphotericin B and itraconazole,	Resolved after 4 weeks therapy
2004/2005 [14]	69	F	Corneal transplantation	Keratitis	7 Months	Remove the corneal button and repeat transplant	Healed
/2007 [15]	44	M	Immunosuppressive therapy because of Still's disease	Lung	6 Months	Amphotericin B	Death after 10 days therapy
2012/2013 [16]	55	M	Liver transplant	Blood	34 Days	Posaconazole, remove central venous catheter	Survived
Present case 2013	31	M	AIDS	Cerebrospinal fluid	2 Weeks	Fluconazole	Death within 2 days

been a total of 21 cases of *C. albidus* extra-dermal infection in humans. Psychiatric history, chronic steroid exposure, organ transplantation, hematonosis, 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 *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 *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), hematopathy (1 case) and exposure to pigeon excrement (1 case). Present case is the first *C. albidus* intracranial infection due to AIDS.

C. albidus infection has similar clinical manifestations as other cryptococci 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 *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 *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 *C. albidus* is the pathogen. Those all help the diagnosis of *C. albidus* encephalitis. Patient show no fever probably result from the immunosuppression caused by AIDS.

The treatment for *C. albidus* is not well defined. Amphotericin B has been modestly effective in the treatment of *C. albidus*. *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) *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

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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