Int J Clin Exp Med 2016;9(3):6926-6930
www.ijcem.com /ISSN:1940-5901/IJCEM0019569

Case Report

Cryptococcal meningitis in an immunocompetent patient: a case report and review of the literatures

Shan-Shan Li[1,2,3], Xin-Yue Tang[1,2,3], Sheng-Guo Zhang[1,2,3], Shun-Lan Ni[1,2,3], Nai-Bin Yang[1,2,3], Ming-Qin Lu[1,2,3]

[1]Department of Infection Disease, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang, P. R. China; [2]Wenzhou Key Laboratory of Hepatology, Wenzhou 325000, Zhejiang, P. R. China; [3]Institute of Hepatology, Wenzhou Medical University, Wenzhou 325000, Zhejiang, P. R. China

Received November 11 2015; Accepted January 23 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: Cryptococcal meningitis is an opportunistic infection in immunosuppressed hosts with high morbidity and mortality. Once suffering from cryptococcal meningitis, immunocompetent patients are more likely to achieve poor outcome, because of the powerful immune response. Here we present a case of cryptococcal meningitis occurring in an immunocompetent host with no definite underlying diseases and no history of taking immunosuppressive agents. We highlight the importance of timely diagnosis and optimal treatment of the cryptococcal infection in immunocompetent patients.

Keywords: Cryptococcal meningitis, immunocompetent, fluconazole, prognosis

Introduction

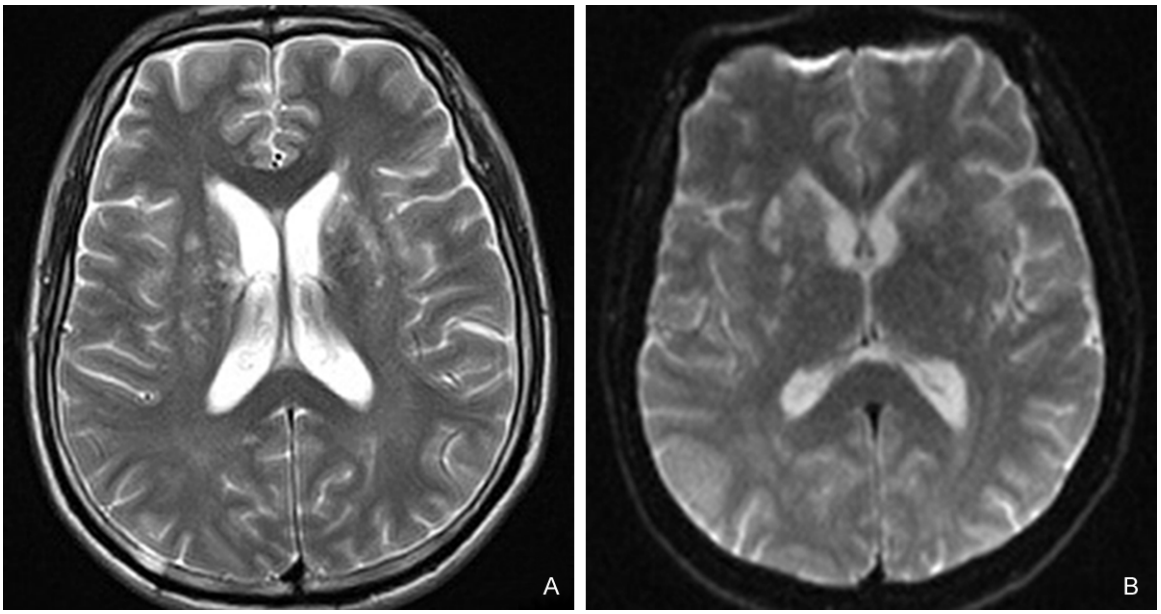
Cryptococcal meningitis, caused by the Cryptococcus neoformans, a ubiquitous environmental fungus, is a fatal HIV-related opportunistic infection. With the enhancement of the relevance ratio and recognition of its life-threating effect, cryptococcal meningitis draws more and more clinicians' attention. According to the official statistics, there are approximately one million new cases each year worldwide and the lethality is more than 50 percent [1, 2]. The high morbidity and a need of long-term treatment increase the economic and medical burden in sub-Saharan Africa and Southeast Asia, the most heavily affected areas [1].

As an encapsulate yeast, C. neoformans can be constantly found in soil, pigeon feces, milk and human beings' oral cavity as well [3]. It usually invades the immunocompromised hosts through respiratory tract and damaged skins exposure to pigeon feces, leading to the varied infection: pulmonary cryptococcosis, skin nodules, cryptococcal meningitis, cryptococcus bacteremia, etc [3].

C. neoformans frequently causes opportunistic infections in immunocompromised patients with underlying diseases, such as HIV, solid organ transplantation, liver cirrhosis, tuberculosis, SLE and other diseases which need the long-term therapy of immunosuppressive agent [1, 3]. However, immunocompetent hosts are rarely reported to get cryptococcal infection. It is easy to make a misdiagnosis as viral or bacterial meningitis, when immunocompetent patient manifests with headache, fever and other altered mental status [4]. Therefore, the early confirmation calls for accumulated clinical experience and sensitive laboratory tests.

Case report

A 39-year-old Chinese male, a native of Wenzhou and working as an office clerk, visited our hospital with a complaint of persistent terrible headache and a fever with the temperature waving around 39 degree centigrade for nearly a month. His examination of Magnetic Resonance Imaging of brain in other hospital indicated the cerebral edema and diffused abnormal signal in the occipitotemporal convolutions and basal ganglia (**Figure 1**). He denied vomit, twitch, coma, visual disturbance, weight loss or any other symptoms originally, and the past medical history revealed that he was healthy with no history of alcoholism, hypertension, dia-



Firgue 1. MRI of brain in February 2015 demonstrated (A) hyperintense signal in basal ganglia region, (B) diffused brain edema in on T2-weighted images.

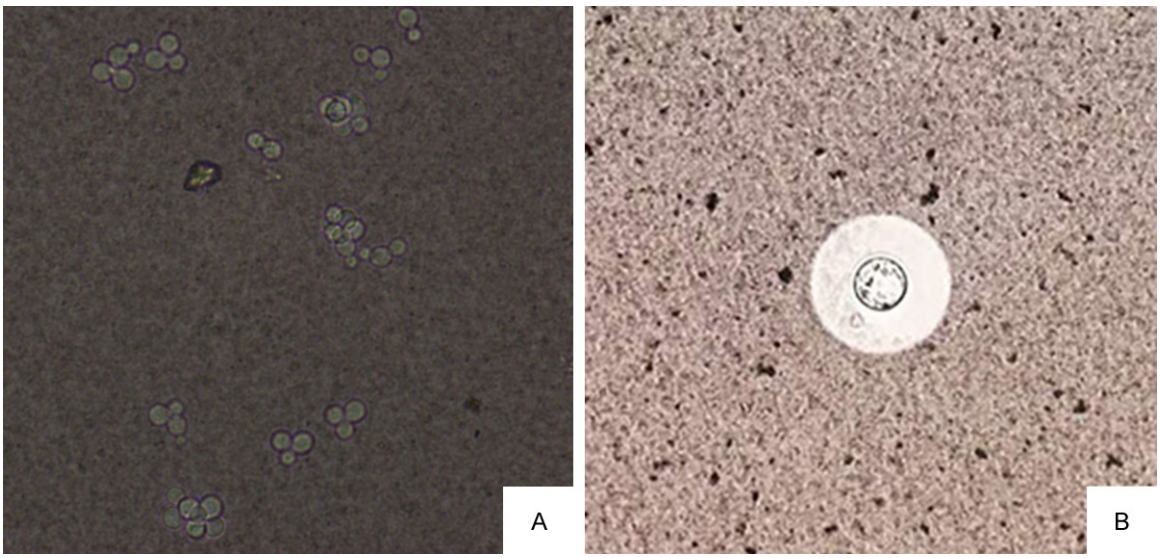
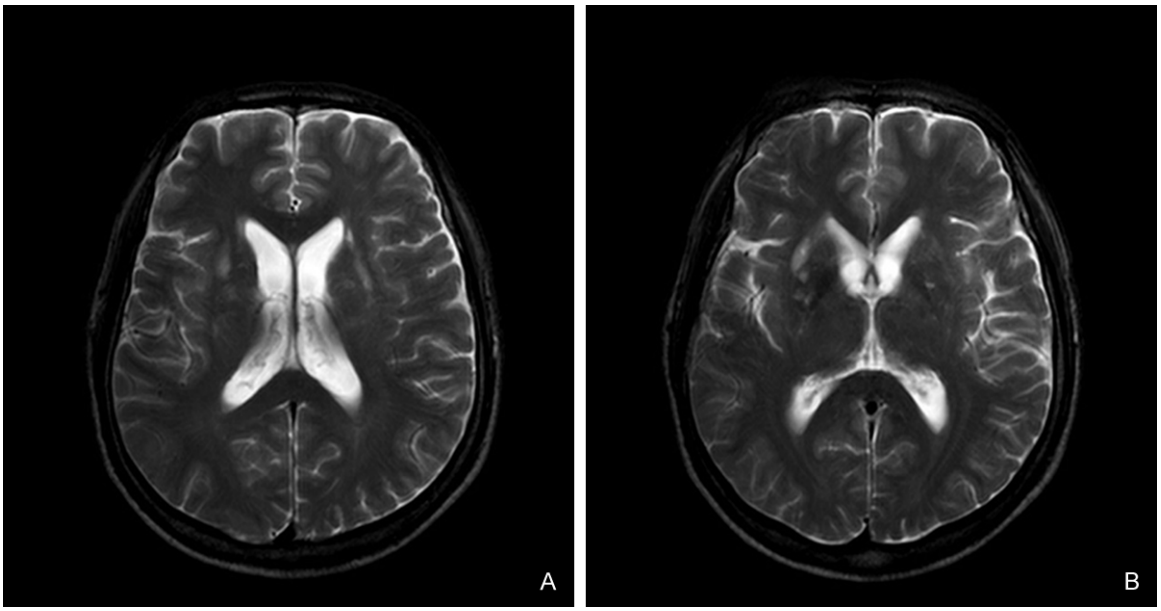


Figure 2. Microscopy of CSF at second lumbar puncture. (A) C. neoformans with indian ink staining (B) capsule of the C. neoformans.

betes, liver diseases, sarcoidosis or taking any immunosuppressive drugs.

On physical examination he had a body temperature of 39.3 degree centigrade, blood pressure 135/70 mmHg and a regular pulse of 78 beats/min. The color of his mucous membrane and skin were normal without rash or herpes. And his physical examination of heart and lungs as well as pupillary light reflex showed normal. Although the Babinski's sign and Kerning's sign were negative, his stiff-neck was suspicious.

His original blood routine and biochemical analysis revealed no abnormality: erythrocyte 4.33*10^9/mm^3, leukocyte 5.87*10^6/mm^3, the percentage of monocyte 15.4%, platelet 246*10^6/mm^3, hemoglobin 13.3 g/dl, albumin 45 g/l, glucose 5.6 mmol/l, normal renal



Firgue 3. MRI of brain in April 2015 showed (A) hyperintense signal in basal ganglia and (B) brain edema in occipital region ameliorated obiviously compare to the February one on T2-weighted images.

and liver function. There was no suspicious tumor marker, and no HIV, hepatitis B, hepatitis C and syphilis as well. The initial lumbar puncture reveled: leukocyte 200*10^3/mm^3, proteins 77 g/l, chloridum 114 mmol/l, no organism founded.

Without any accurate evidence of cryptococcal meningitis infection, he was treated empirically with mannitol to alleviate intracranial pressure, acyclovir and ceftriaxone sodium for viral meningitis and bacterial meningitis, respectively. However, there was no clinic improvement, and he began to lose his consciousness and the temperature was barely normal. Fortunately, the second lumbar puncture report indicated that Cryptococcus neoformans was found in high power field of vision, he was confirmed of cryptococcal meningitis (**Figure 2**). Immediately, he started to receive the intravenous administration of amphotericin B 0.7 mg/kg/day and take flucytosine orally 1.0 g/day. While, after 2 weeks of antifungal treatment, the following biochemical analysis suggested renal dysfunction and liver injury: serum creatinine 110 umol/l, alkaline phosphate 82 u/l, γ-glutamyl transferase 50 u/l. Considering the amphotericin B's renal toxicity and hepatotoxicity, we chose the fluconazole 400 mg/day intravenously combing with flucytosine for the following therapy. At week 4, he failed to obtain obvious clinic improvement and the third lumbar puncture result showed that cryptococcal capsular polysaccharide antigen was 1:128 without organism found. What's worse, he began to be disturbed with blurred vision, and the retina angiograph indicated retinitis and choroid plexus space-occupying lesions. As his creatinine clearance rate was almost approaching normal, we increased the dose of fluconazole to 600 mg at week 4, after which his symptoms slowly alleviated. At week 8, the fourth lumbar puncture result indicated that cryptococcus antigen was still positive although culture result showed negative. We continued the combination of fluconazole 600 mg intravenously and flucytosine orally taken 1.0 g per day for consolidation therapy. At week 18, even though the patient still complained about slightly reduced visual acuity, he got no headache and any other discomfort. As the MRI report of brain also revealed the improvement (**Figure 3**), we started the treatment of fluconazole 400 mg and flucytosine 1.0 g orally taken per day. At week 20, the fifth lumber puncture indicated negative result and he began to receive the prophylactic application of sole oral fluconazole 400 mg/day. After the patient discharged, he was under close monitoring and visited the follow-up clinic regularly for six months.

Discussion

This case highlights the importance of timely confirmation and optimal antifungal treatment of immunocompetent hosts' cryptococcal men-

ingitis infections. Cryptococcal meningitis often begins with nonspecific clinical manifestations such as headache, dispirited and fever, hardly correlate to cryptococcal infection [4]. Therefore, the early diagnosis relies on the laboratory tests, imageology character and clinical experience. Even though the positive culturing result of the organism in cerebrospinal fluid is regard as the golden standard for diagnosis of cryptococcal meningitis. It requires precise laboratory infrastructures and skilled technicians, the same as the microscopy of the organism, which are difficult for the resource-limited countries [5]. On the other hand, its poor sensitivity is likely to result in the misdiagnosis. In this case, we took the latex agglutination test (LA test) to detect the cryptococcal capsular polysaccharide antigen in the blood and CSF in addition to culturing and microscope. The LA test, widely used in developed regions, is more sensitive and convenient than microscopy of the organism, which is still too expensive for the developing countries. In recent published literatures, another new diagnostic method-lateral flow immunochromatographic assay (LFA) is recommended, which is more cost-effective, just requiring a drop of blood or CSF, only taking ten minutes to report and can be shipped at room temperature [6]. So LFA is more suitable for diagnosis of cryptococcal meningitis in the sub-Saharan Africa and Southeast Asia, where most of the world's cryptococcosis occur [5, 6].

Comparing to the accurate diagnosis, early establishment of appropriate antifungal treatment is more important for improving the prognosis. Because of the suboptimal initial antifungal treatment and intense host immune response, the immunocompetent patients with cryptococcus infections are more likely to experience poor outcome [4]. However, the exact influence of normal immune response in the prognosis of cryptococcal meningitis is not clear yet [2]. So clinicians should be familiar with treatment guidelines and know the indication and contraindication of each antifungal drug well.

According to the Infection Disease Society of America (IDSA) guidelines, the combination of Amphotericin B and flucytosine is recommended for the treatment of induction phase [7, 8]. But the prolong treatment of Amphotericin B will lead to renal failure, inevitably. The secondary reaction also occurs in this case, so we chose the combination of fluconazole and flucytosine instead. Even though the drug resistance and poor organism clearance of fluconazole are frequently reported, the combination achieved success in this case at last. Except those conversant antifungal agents, recent published literatures reveal that voriconazole is excellent in vivo activity against C. neoformans with good CSF penetration [9, 10]. And it contributes to the reduction of fungal load and prolonged survival in the animal disease models of CM [10]. Itraconazole is effective for cryptococcus clearance as well and less resistance reported in tests in vitro than fluconazole [11]. Due to its poor penetration into central nervous system, itraconazole is rarely recommended for the routine therapy of cryptococcal infection [12]. In the future, individual therapy would be carried out on the basis of the characteristic result of fungal susceptibility and resistance.

Although cryptococcal meningitis infection is rare among immunocompetent patients, the delayed diagnosis and suboptimal treatment result in the poor prognosis and high mortality. So we outline the importance of suspicion for cryptococcal infection in immunocompetent patients with subtle clinical presentation.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ming-Qin Lu, Department of Infection Disease, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou Key Laboratory of Hepatology, Institute of Hepatology, Wenzhou Medical University, Nanbaixiang Street, Ouhai District, Wenzhou 325000, Zhejiang, P. R. China. E-mail: lmq0906@163.com

References

[1] Lin YY, Shiau S and Fang CT. Risk factors for invasive Cryptococcus neoformans diseases: a case-control study. PLoS One 2015; 10: e0119090.

[2] Panackal AA, Wuest SC, Lin YC, Wu T, Zhang N, Kosa P, Komori M, Blake A, Browne SK, Rosen LB, Hagen F, Meis J, Levitz SM, Quezado M, Hammoud D, Bennett JE, Bielekova B and Williamson PR. Paradoxical Immune Responses in Non-HIV Cryptococcal Meningitis. PLoS Pathog 2015; 11: e1004884.

[3] O'Meara TR and Alspaugh JA. The Cryptococcus neoformans capsule: a sword and a shield. Clin Microbiol Rev 2012; 25: 387-408.

[4] Louro R, Ferreira R, Pinheiro C, Parada H, Faria D and Monteiro E. Fungal meningitis in an im-

munocompetent patient. Clin Drug Investig 2013; 33 Suppl 1: S47-50.
[5] Tang MW, Clemons KV, Katzenstein DA and Stevens DA. The cryptococcal antigen lateral flow assay: A point-of-care diagnostic at an opportune time. Crit Rev Microbiol 2015; 1-9.
[6] Kabanda T, Siedner MJ, Klausner JD, Muzoora C and Boulware DR. Point-of-care diagnosis and prognostication of cryptococcal meningitis with the cryptococcal antigen lateral flow assay on cerebrospinal fluid. Clin Infect Dis 2014; 58: 113-116.
[7] Day JN, Chau TT, Wolbers M, Mai PP, Dung NT, Mai NH, Phu NH, Nghia HD, Phong ND, Thai CQ, Thai le H, Chuong LV, Sinh DX, Duong VA, Hoang TN, Diep PT, Campbell JI, Sieu TP, Baker SG, Chau NV, Hien TT, Lalloo DG and Farrar JJ. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med 2013; 368: 1291-1302.
[8] Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, Harrison TS, Larsen RA, Lortholary O, Nguyen MH, Pappas PG, Powderly WG, Singh N, Sobel JD and Sorrell TC. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis 2010; 50: 291-322.
[9] Yao Y, Zhang JT, Yan B, Gao T, Xing XW, Tian CL, Huang XS and Yu SY. Voriconazole: a novel treatment option for cryptococcal meningitis. Infect Dis (Lond) 2015; 47: 694-700.
[10] Gazzoni AF, Capilla J, Mayayo E and Guarro J. Efficacy of intrathecal administration of liposomal amphotericin B combined with voriconazole in a murine model of cryptococcal meningitis. Int J Antimicrob Agents 2012; 39: 223-227.
[11] Loyse A, Wilson D, Meintjes G, Jarvis JN, Bicanic T, Bishop L, Rebe K, Williams A, Jaffar S, Bekker LG, Wood R and Harrison TS. Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis. Clin Infect Dis 2012; 54: 121-128.
[12] Trpkovic A, Pekmezovic M, Barac A, Crncevic Radovic L and Arsic Arsenijevic V. In vitro antifungal activities of amphotericin B, 5-fluorocytosine, fluconazole and itraconazole against Cryptococcus neoformans isolated from cerebrospinal fluid and blood from patients in Serbia. J Mycol Med 2012; 22: 243-248.