CASE REPORT

Liposomal amphotericin B for a case of intractable cryptococcal meningoencephalitis and immune reconstitution syndrome

Atsushi Sasakawa*, Yoshihiko Yamamoto*, Keishiro Yajima*, Mio Sakai**, Tomoko Uehira*, Takuma Shirasaka*, and Toshio Makie*

*AIDS Medical Center and **Department of Radiology ; National Hospital Organization, Osaka National Hospital, Osaka, Japan

Abstract : We examined the efficacy of liposomal amphotericin B (L-AMB) for intractable cryptococcal meningoencephalitis in a patient with acquired immunodeficiency syndrome (AIDS) and the presence of immune reconstitution syndrome (IRS) caused by the treatment. A 34-year-old patient presented with meningitis. Cryptococcal organisms were detected microscopically in the cerebrospinal fluid (CSF) with Indian ink staining, and were then cultured from the CSF. Initial treatment with amphotericin B and flucytosine (5-FC) or voriconazole and/or fluconazole failed to eradicate cryptococcal organisms from the CSF. Secondary treatment with L-AMB and 5-FC following seven months of antiretroviral therapy was successful. Simultaneously, treatment with L-AMB caused severe brain edema likely due to IRS. There were large differences in immune function improvement and liposomalization of the fungicide between the initial and secondary treatments. In conclusion, differences in immune status should be considered when administering L-AMB, in order to prevent IRS-related complications. J. Med. Invest. 55 : 292-296, August, 2008

Keywords **:** *AIDS-related opportunistic infections, cryptococcus, immune reconstitution syndrome (IRS), liposomal amphotericin B*

INTRODUCTION

Although highly active antiretroviral therapy (HAART) has dramatically reduced the incidence of opportunistic illnesses and substantially extended lifespan in patients with acquired immunodeficiency syndrome (AIDS) (1, 2), complications of central nervous system (CNS) infections remain a major cause of morbidity and mortality. Cryptococcal meningitis is one of the most frequent forms of meningoencephalitis among AIDS patients (3-5). Moreover, its high mortality rate has not improved (6) even with high-dose amphotericin B (AMPH-B) treatment (7). More recently, liposomal amphotericin B (L-AMB) has emerged as a new fungicide to combat cryptococci. We used this newly approved fungicide in a case of intractable cryptococcal meningoencephalitis in which treatment with AMPH-B and flucytosine (5-FC), and then with voriconazole (VRCZ) and/or fluconazole (FLCZ), failed to eradicate cryptococcal organisms from the cerebrospinal fluid (CSF). Although the treatment finally succeeded in clearing cryptococci from the CSF, it simultaneously caused brain edema secon-

Received for publication January 5, 2008 ; accepted April 15, 2008.

Address correspondence and reprint requests to Toshio Makie, MD, PhD, Office of New drug IV Pharmaceuticals and Medical Divices Agency, Shin-kasumigaseki Building. 3-3-2, Kasumigaseki, Chiyoda-ku, Tokyo 100-0013, Japan and Fax : +81-3-3506-9453.

dary to immune reconstitution syndrome (IRS) (8). The objective of the present case study was to evaluate the efficiency of L-AMB for treating intractable cryptococcal meningoencephalitis. In addition, the presence of IRS in response to L-AMB treatment was examined.

CASE REPORT

Patient presentation and laboratory findings

A 34-year-old woman with a diagnosis of AIDS and cryptococcal meningoencephalitis was transferred to the AIDS Medical Center, Osaka National Hospital, Japan. On admission, physical examination revealed diplopia, severe neck rigidity, and a body temperature persisting at over 38.5°C. Her mental status was drowsy but oriented, and she complained of severe headache. CD4+ and CD8+ T-cell counts were 13 and 270/μl, respectively, with a viral load of 180×10^3 copies/μl. Hepatic and renal function data were within normal ranges, as were the white blood cell count and the level of C-reactive protein. The serum cryptococcal C antigen level was elevated 65,536-fold, and the CSF pressure was remarkably high at 53 cm H_2O. The CSF glucose level was slightly low (Fig. 1). Cryptococcal organisms were confirmed in biopsy material from a cervical lymph node, detected microscopically in the CSF by Indian ink staining, and observed in CSF cultures.

Magnetic resonance imaging (MRI) of the head revealed the diffuse vascular enhancement characteristic of meningitis. Multiple small lesions, consistent with a diagnosis of cryptococcal meningitis, were demonstrated in T2-weighted images at bilateral basal nuclei. However, MRI showed no partial inflammatory lesions.

Clinical course

Sets of AMPH-B (30 mg/day, 0.7 mg/kg × 43 kg) and 5-FC (1000 mg, q6h), and sets of VRCZ (320 mg/day) and/or FLCZ (400 mg/day) were used alternately for 2.5 months (Fig. 1). The first trials of AMPH-B and 5-FC were interrupted due to acute thrombocytopenia after the initial week. The high CSF pressure and headache did not improve even upon administration of VRCZ and FLCZ, whose concentrations in the CSF were 2.0 and 27.7 μg/ml, respectively. The CSF pressure decreased from 53 to 20 cm H_2O by retrial of AMPH-B and 5-FC at slightly lower doses ; however, cryptococcal organisms continued to persist in the CSF. With improvement of clinical presentations, namely headache and diplopia, the patient was treated with HAART, consisting of tenofovir (TDF ; 300 mg, qd), emtricitabine (FTC ; 200 mg, qd), and efavirenz (EFV ; 600 mg, qd). The antifungal drug was changed to FLCZ (400 mg, qd) for maintenance therapy. Two months from the initiation of this therapy, the patient was discharged due to improving clinical presentations, although cryptococcal organisms still remained in the CSF.

After seven months of antiretroviral therapy, the patient reported worsening noise in her ears and

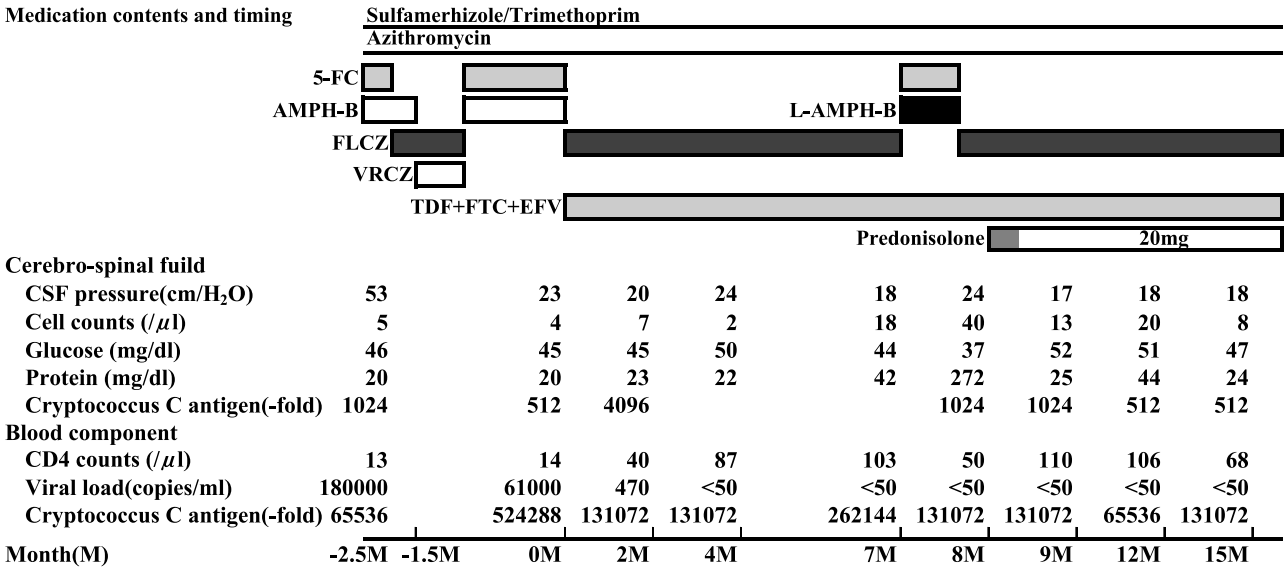

Fig. 1. Medication regimen and laboratory data during the clinical course. Prednisolone treatment included pulse therapy with methylprednisolone (500 mg/day) for the first three days.

frequent headache, and MRI revealed partial inflammatory lesions (Fig. 2a). IRS with immune restoration was not suspected at the site of the lesions because of a rising CD4 cell count of 103/μl. The patient was readmitted to the hospital a second time for treatment, with cryptococci present in the CSF. She received 5-FC (1,000 mg, q8h) and the newly approved L-AMB (150 mg/day). Treatment was continued for 12 days, but was then stopped due to severe nausea and headache. MRI suggested stem herniation due to a large area of inflammatory hyperintensity on T2-weighted images (Fig. 2b) and deformation of the fourth cerebral ventricle. Immediate steroid pulse therapy was conducted to suppress inflammation and glycerol was used to reduce the cerebral pressure, since brain edema secondary to immune reconstitution syndrome (IRS) had rapidly advanced. Steroid pulse therapy drastically reduced the edema. Subsequently, cryptococcal organisms were undetectable in the CSF in four tests, even at 15 months. However, inflammation with brain edema appeared again when the steroid dose was lowered to less than 20 mg.

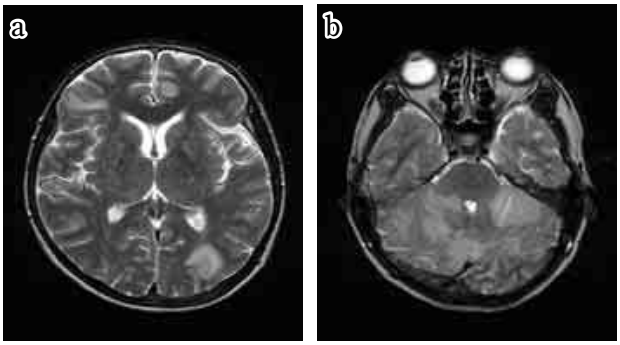

Fig. 2. T2-weighted MRI images. The condition of the two images has been unified in terms of the window width. (a) Before the second treatment, a spotty inflammatory hyperintensity on T2-weighted images appeared in the occipital area. (b) After treatment, an inflammatory hyperintensity indicated a large area of brain edema.

DISCUSSION

We report a case of intractable cryptococcal meningoencephalitis in which administration of L-AMB eradicated the cryptococcal infection. Simultaneously, treatment with L-AMB caused brain edema secondary to IRS. This clinical presentation clearly coincides with the four conditions of IRS : HAART, clinical evidence of an inflammatory process inconsistent with the usual course of cryptococcosis, a rising CD4 cell count, and falling HIV-1 RNA levels (8). In IRS, a memory mechanism of the pathogen in opportunistic diseases is thought to contribute to symptom deterioration in the process of immune restoration (8-14). IRS associated with cryptococcus frequently emerges in the early stages of treatment after introducing HAART. However, IRS sometimes recurs after six months or more (9, 14). The present case is valuable when considering a mechanism of IRS because the association between the timing of deterioration and its cause can be clearly explained. It is a big clue that steroid therapy was effective to the brain edema of this case. The related reaction indicates that a new immune reaction occurred after treatment with L-ABM and the steroid suppressed it. The synthesized mechanism, including delayed IRS, will be discussed below.

There were key differences between the initial and secondary treatments in relation to improvements in the patient's immune function and liposomalization of AMPH-B. During the first treatment, macrophages that eradicate fungal invasion (15, 16), may be inactivated by HIV (17). This inactivation of the macrophages can reduce the efficacy of an azole drug in suppressing meningoencephalitis since the mode of action for azoles is fungistatic rather than fungicidal. Indeed, the two azole drugs used were ineffective in spite of sufficient penetration into the CSF. During the second treatment, it is believed that macrophages were activated because HAART suppressed HIV. Moreover, L-AMB treatment has several advantages over conventional antifungal drugs. L-AMB has the potential to cross the blood-brain barrier (18, 19), whereas AMPH-B does not. Furthermore, liposomalization markedly decreases the cytotoxicity of AMPH-B, making high-dose administration possible. When vascular permeability is exacerbated by infection, L-AMB concentrates locally around infectious lesions, at a level more than 15 times higher than AMPH-B (20-22). Indeed, the secondary treatment eradicated the cryptococcal infection fungicidally. However, the activation of macrophages would likely have been unstable even if the new immune response eradicated cryptococcus organisms. The following brain edema needed to be suppressed by steroid therapy in our patient. Steroids suppress the immune response and therefore can be effective in preventing IRS (12, 23).

L-AMB was successful in eradicating intractable cryptococcal infections, but treatment with L-AMB simultaneously caused IRS. However, L-AMB should be used with caution, with differences in

immune status taken into consideration in order to prevent IRS.

ACKNOWLEDGMENTS

This study was supported by Grant-in-Aid for Scientific Research Number 80435891. We thank Kanako Hamasaki and Mayuko Uota for coordination of the authors.

REFERENCES

1. Sepkowitz KA : AIDS–the first 20 years. N Engl J Med 344(23) : 1764-1772, 2001
2. McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW : Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. AIDS 13 : 1687-1695, 1999
3. Dromer F, Mathoulin-Pélissier S, Fontanet A, Ronin O, Dupont B, Lortholary O : Epidemiology of HIV-associated cryptococcosis in France (1985-2001) : comparison of the pre- and post-HAART eras. AIDS 18(3) : 555-562, 2004
4. Del Valle L, Pina-Oviedo S : HIV disorders of the brain : pathology and pathogenesis. Front Biosci 11 : 718-732, 2006
5. Collazos J : Opportunistic infections of the CNS in patients with AIDS : diagnosis and management. CNS Drugs 17(12) : 869-887, 2003
6. Corbett EL, Churchyard GJ, Charalambos S, Samb B, Moloi V, Clayton TC, Grant AD, Murray J, Hayes RJ, De Cock KM : Morbidity and mortality in South African gold miners : impact of untreated disease due to human immunodeficiency virus. Clin Infect Dis 34(9) : 1251-1258, 2002
7. van der Horst CM, Saag MS, Cloud GA, Hamill RJ, Graybill JR, Sobel JD, Johnson PC, Tuazon CU, Kerkering T, Moskovitz BL, Powderly WG, Dismukes WE : Treatment of cryptococcal meningoencephalitis associated with the acquired immunodeficiency syndrome. N Engl J Med 337(1) : 15-21, 1997
8. Shelburne SA 3rd, Darcourt J, White AC Jr, Greenberg SB, Hamill RJ, Atmar RL, Visnegarwala F : The role of immune reconstitution inflammatory syndrome in AIDS-related *Cryptococcus neoformans* disease in the era of highly active antiretroviral therapy. Clin Infect Dis 40(7) : 1049-1052, 2005
9. Woods ML II, MacGinley R, Eisen DP, Allworth AM : HIV combination therapy : partial immune restitution unmasking latent cryptococcal infection. AIDS 12 : 1491-1494, 1998
10. DeSimone JA, Pomerantz RJ, Babinchak TJ : Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. Ann Intern Med 133 : 447-454, 2000
11. Lipman M, Breen R : Immune reconstruction inflammatory syndrome in HIV. Curr Opin Infect Dis 19 : 20-25, 2006
12. Skiest DJ, Hester LJ, Hardy RD : Cryptococcal immune IRIS : report of four cases in three patients and review of the literature. J Infect 51(5) : e289-297, 2005
13. Broom J, Woods M II, Allworth A : Immune reconstitution inflammatory syndrome producing atypical presentations of cryptococcal meningoencephalitis : case report and a review of immune reconstitution-associated cryptococcal infections. Scand J Infect Dis 38(3) : 219-221, 2006
14. Lortholary O, Fontanet A, Mémain N, Martin A, Sitbon K, Dromer F : Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS 19(10) : 1043-1049, 2005
15. Lieberman J, Shankar P, Manjunath N, Andersson J : Dressed to kill? A review of why antiviral CD8 T lymphocytes fail to prevent progressive immunodeficiency in HIV-1 infection. Blood 98(6) : 1667-1677, 2001
16. Shibuya K, Hirata A, Omuta J, Sugamata M, Katori S, Saito N, Murata N, Morita A, Takahashi K, Hasegawa C, Mitsuda A, Hatori T, Nonaka H : Granuloma and cryptococcosis. J Infect Chemother 11(3) : 115-122, 2005
17. X Bai, J-D Chen, A-G Yang, F Torti, S-Y Chen : Genetic co-inactivation of macrophage- and T-tropic HIV-1 chemokine coreceptors CCR-5 and CXCR-4 by intrakines. Nature 5 (7) : 984-994, 1998
18. Adler-Moore J, Proffitt RT : Effect of tissue penetration on AmBisome efficacy. Curr Opin Invest Drugs 4(2) : 179-185, 2003
19. Takemoto K, Yamamoto Y, Ueda Y : Influence of the progression of cryptococcal meningitis on brain penetration and efficacy of AmBisome in a murine model. Chemotherapy 52(6) : 271-278, 2006

20. Deray G : Amphotericin B nephrotoxicity. J Antimicrob Chemother 49 (Suppl. 1) : 37-41, 2002
21. Adler-Moore JP, Chiang SM, Satorius A, Guerra D, McAndrews B, McManus EJ, Proffitt RT : Treatment of murine candidosis and cryptococcosis with a unilamellar liposomal amphotericin B formulation (AmBisome). J Antimicrob Chemother 28 (Suppl. B) : 63-71, 1991
22. Takemoto K, Yamamoto Y, Ueda Y, Sumita Y, Yoshida K, Niki Y : Comparative study on the efficacy of AmBisome and Fungizone in a mouse model of pulmonary aspergillosis. J Antimicrob Chemother 57(4) : 724-731, 2006
23. Venkataramana A, Pardo CA, McArthur JC, Kerr DA, Irani DN, Griffin JW, Burger P, Reich DS, Calabresi PA, Nath A : Immune reconstitution inflammatory syndrome in the CNS of HIV-infected patients. Neurology 67(3) : 383-388, 2006