

TREATMENT OF TOXOPLASMA BRAIN ABSCESS WITH CLINDAMYCIN AND SULFADIAZINE IN AN AIDS PATIENT WITH CONCURRENT ATYPICAL PNEUMOCYSTIS CARINII PNEUMONIA

Hung-Chin Tsai,^{1,3} Susan Shin-Jung Lee,² Hsi-Hsun Lin,² Wei-Ru Lin,² Yao-Shen Chen,² Chun-Kai Huang,² Yung-Ching Liu,² and Eng-Rin Chen³

Abstract: Toxoplasmosis is the most common opportunistic infection of the central nervous system in patients with AIDS. The standard treatment for toxoplasmic encephalitis is pyrimethamine and sulfadiazine. There have been few reports of concurrent *Toxoplasma* brain abscess and cavitary *Pneumocystis carinii* pneumonia (PCP) in Taiwan. We report the case of a 26-year-old homosexual man with coexisting infection with *Toxoplasma gondii* and *P. carinii* who was successfully treated for brain abscess with clindamycin and sulfadiazine. The cavitary lung lesions, initially diagnosed as pulmonary tuberculosis, were proved to be PCP by lung biopsy. HIV infection and syphilis had been diagnosed 1 year before admission. He presented with general weakness, ataxia, nausea, blurred vision and fever for 2 weeks. Magnetic resonance imaging of the brain revealed multiple ring-enhanced lesions over the cerebrum and cerebellum. Chest roentgenography showed a 3-cm lesion with cavitation over the right upper lung field. Diagnostic computerized tomography-guided lung biopsy revealed *P. carinii* cysts. Clindamycin, sulfadiazine and trimethoprim (TMP)-sulfamethoxazole (20 mg/kg/day TMP) were given with good response. His CD4 count rose from 40 to 280/ μ L 4 months later. All antibiotics were discontinued after 4.5 months due to the development of a skin rash. He was well at follow-up 1 year later. This case suggests that the combination of clindamycin and sulfadiazine is an effective treatment for *Toxoplasma* brain abscess and highlights the importance of diagnostic lung biopsy for cavitary lung lesions, particularly in a region endemic for tuberculosis.

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Toxoplasma brain abscess is the most common cause of cerebral mass lesions in AIDS patients. *Toxoplasma gondii* is commonly acquired through ingestion of contaminated meats, resulting in latent infection. In most instances, toxoplasmic encephalitis develops when the CD4 cell count falls below 100/ μ L [1]. The incidence of toxoplasmic encephalitis is therefore directly proportional to the prevalence of antibodies to *Toxoplasma* in any given population [2]. At present, treatment of toxoplasmic encephalitis is usually initiated

upon presumptive diagnosis, and the clinical diagnosis is usually based on typical imaging findings, positive serology, and clinical and roentgenographic response to specific therapy. The standard treatment for toxoplasmic encephalitis is pyrimethamine/sulfadiazine, although clindamycin is sometimes used in place of sulfadiazine. We report the case of an AIDS patient with concurrent *Pneumocystis carinii* pneumonia (PCP) and *Toxoplasma* brain abscess. The brain abscess was treated successfully with clindamycin and sulfadiazine.

¹Department of Medicine, Wan-Chiau Veterans Hospital, Kaohsiung; ²Section of Infectious Diseases, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, and National Yang-Ming University, Taipei; ³Department of Parasitology and Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung.

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Reprint requests and correspondence to: Dr. Yung-Ching Liu, Section of Infectious Diseases, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung, Taiwan.

Case Report

This 26-year-old homosexual man visited our hospital on December 20th, 1999, with the chief complaints of general weakness, ataxia, nausea, blurred vision and fever for 2 weeks. HIV infection and syphilis had been diagnosed when he visited our outpatient department 1 year before this admission; since then, he had been lost to follow-up. At admission, blood pressure was 114/72 mmHg, pulse rate 90/minute, and temperature 36.5°C. Consciousness was clear, and chest and abdominal examinations were unremarkable. Examination of the ocular fundi revealed cotton wool spots. Cerebellar signs and other neurologic examinations were normal except for a positive Romberg test. Laboratory tests revealed a white cell count of $4.11 \times 10^9/L$ with 60% granulocytes, 23% lymphocytes, 11% monocytes and 5% eosinophils. Platelet count was $121 \times 10^9/L$. CD4 count was 40/ μL and HIV viral load was more than 500,000 copies/mL (Quantiplex HIV-1 RNA 3.0 bDNA assay, Chiron Diagnostics Corporation, East Walpole, MA, USA). Chest roentgenography showed a 3-cm cavitory lesion over the right apical region (Fig. 1). Brain computerized tomography (CT) scan disclosed a low density over the cerebellum, basal ganglion and left occipital area. Analysis of the cerebrospinal fluid (CSF) after lumbar puncture showed a white cell count of 2/ μL , red blood cell count of 7/ μL , protein concentration of 1.63 g/L, and glucose concentration of 3.72 mmol/L (simultaneous plasma sugar, 7.16 mmol/L). Gram stain, acid-fast stain and India ink preparation of the CSF and blood culture were all negative. Central nervous system (CNS) toxoplasmosis and pulmonary tuberculosis were suspected and he was admitted. On Day 5 after admission, magnetic



Fig. 1. Chest roentgenogram showing a cavitory lesion over the right upper lung field (arrow).

resonance imaging (MRI) of the brain revealed multiple ring-enhanced lesions ranging from 2 to 8 cm in size over the cerebrum and cerebellum (Fig. 2). Intravenous clindamycin 600 mg every 6 hours and oral sulfadiazine 1 g every 6 hours were administered for presumptive treatment of *Toxoplasma* brain abscess. Serum serologic tests for *T. gondii* were negative. On Day 8 after admission, CT-guided lung biopsy disclosed *P. carinii* cysts on Grocott-Gomori methenamine silver stain. Trimethoprim (TMP)-sulfamethoxazole (SMX) (20 mg/kg/day TMP) was added on Day 11 of admission. MRI of the brain after 2 weeks of treatment showed marked shrinkage of the ring-enhanced lesions (Fig. 3), and his CD4 count rose to 280/ μL after 4 months of treatment with highly active antiretroviral therapy (HAART) and antibiotics. Clindamycin, sulfadiazine and TMP-SMX were discontinued due to development of skin rash after 4.5 months of treatment. At follow-up 1 year later, serologic tests for *Toxoplasma* IgG (Vidas *Toxoplasma* IgG, bioMerieux, Inc, Hazelwood, MO, USA) were positive, he was well, and MRI of the brain showed complete resolution (Fig. 4).

Discussion

Toxoplasmic encephalitis is one of the most common opportunistic infections of the CNS in AIDS patients [3]. It is standard practice to provide empiric treatment for patients infected with HIV who have intracerebral lesions thought to be toxoplasmosis, and to perform a biopsy only in patients who do not show prompt clinical and roentgenographic response to treatment or who have no serologic evidence of previous infection [4]. The mainstay of treatment for toxoplasmic encephalitis is combination chemotherapy with pyrimethamine and sulfadiazine, both of which sequentially block folic acid metabolism and thereby act synergistically against *Toxoplasma*. Folinic acid, which

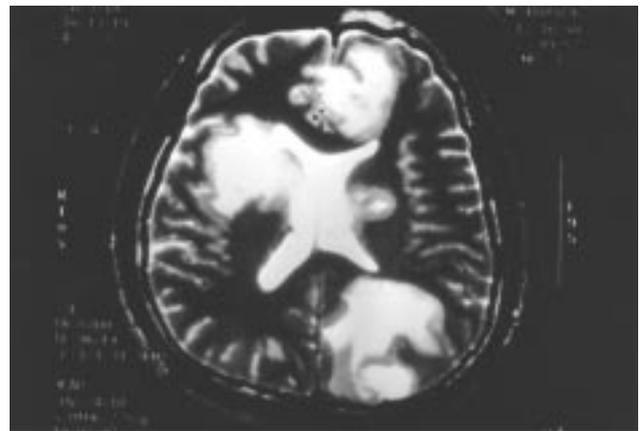


Fig. 2. Axial T2-weighted magnetic resonance image (5300 /96, TR/TE) showing multiple enhancing brain lesions.

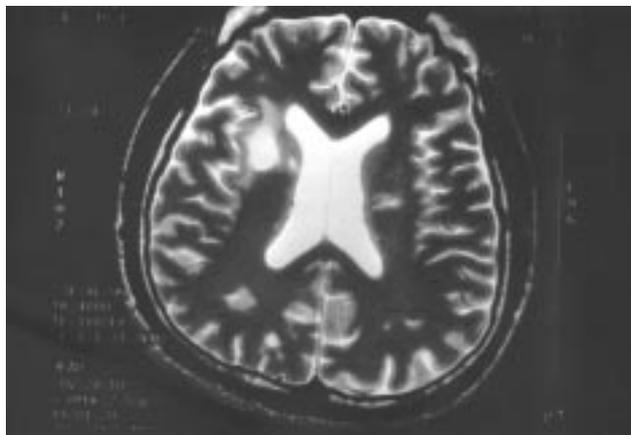


Fig. 3. Magnetic resonance image showing improvement of brain lesions after 2 weeks of anti-toxoplasma therapy.

is preferentially transported across mammalian cell membranes and not across *Toxoplasma* cell membranes, is a useful adjunct that prevents the bone marrow toxicity associated with pyrimethamine [5]. We chose clindamycin and sulfadiazine for the treatment of toxoplasmic encephalitis in this case because pyrimethamine was not available at our hospital or in Taiwan. Although pyrimethamine and sulfadiazine are well absorbed from the gut and both cross the blood–brain barrier, this combination is plagued by high rates of toxicity, which may preclude its use in up to 40% of patients. Use of clindamycin instead of pyrimethamine may decrease the incidence of severe side effects such as bone marrow toxicity. Ease of dosing (clindamycin q6h and sulfadiazine q6h) improves compliance. Folinic acid, which is used to prevent the bone marrow toxicity associated with pyrimethamine, is not required with this treatment. The treatment avoids the need for

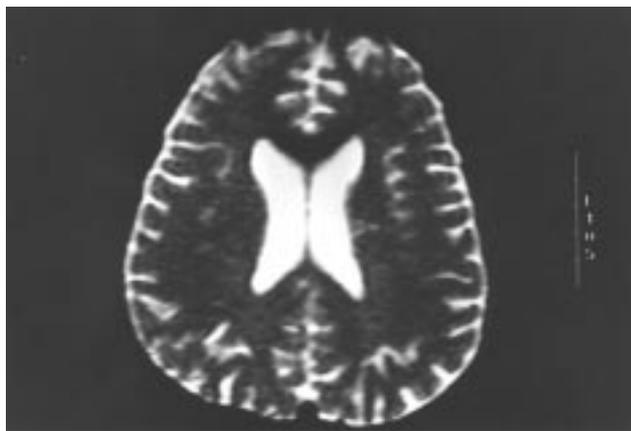


Fig. 4. Magnetic resonance image of the brain showing complete resolution of the abscess at 1-year follow-up.

pyrimethamine, which is associated with erratic levels in the serum and CSF during oral therapy, resulting in difficulties in precise dosing. And most importantly, there is evidence from a variety of animal models showing clear synergy between pyrimethamine or sulfadiazine and chemotherapeutic agents that have no known activity against folate metabolism, including various macrolides, azalides, clindamycin, hydroxynaphthoquinone and doxycycline [6].

The diagnosis of toxoplasmic encephalitis in our patient was based on the clinical and radiographic response to specific anti-toxoplasma therapy. In a study in the USA, Brightbill et al showed that the T2-weighted MRI change from hyperintensity to isointensity in patients treated for toxoplasmic encephalitis can be a function of positive response to antibiotic treatment [7], as in our patient. Although our patient had an initial negative serology (IgG) to *Toxoplasma*, the lack of steroid use during treatment, the continued resolution of brain lesions on MRI at 2-week and 1-year follow-up, and the recent seroconversion of *Toxoplasma* IgG all favor the diagnosis of toxoplasmosis. Negative serum antibodies to *Toxoplasma* at the time of diagnosis of toxoplasmic encephalitis have been reported in the range from less than 3% to 22% [2, 8, 9]. A possible explanation for an initial negative serology would be that our patient was tested before an IgG response could be mounted or while the antibody concentration was too low to be detected by the ELISA kit at our hospital. Batch testing with a different serologic kit confirmed this hypothesis.

The CSF in our patient showed only a mildly elevated protein level without depression of glucose concentration. Because *Toxoplasma* infection predominantly causes encephalitis with little or no meningeal involvement, meningismus is rare, and the CSF change may be subtle.

Although secondary prophylaxis for *T. gondii* is supposed to be lifelong [10], antibiotics were discontinued after 4.5 months in our patient due to the development of a skin rash and evidence of a successful response to HAART (CD4 count rose to 280/ μ L 4 months after treatment). At present, no large, randomized study has supported early discontinuation of secondary prophylaxis for *Toxoplasma*. However, our patient was clinically well at 1-year follow-up, and lesions on brain MRI had completely resolved. The success of treatment in our patient suggests that a study of discontinuation of secondary prophylaxis in selected cases with a high CD4 count might prove it to be safe and cost-effective.

In AIDS patients with PCP infection, unusual and atypical roentgenographic manifestations include unilateral distribution, focal infiltrates, lobar involvement, atelectatic changes, cystic or honeycomb

lesions, nodular densities, hilar enlargement, spontaneous pneumothorax, unilateral hyperlucent lung and pleural effusion, although images may be normal in up to 5% of cases [11]. Cavitation of the lung is an unusual presentation of PCP; therefore, the importance of considering PCP in the differential diagnosis in AIDS patients with a cavitory lung lesion even in the absence of a history of pentamidine prophylaxis should be emphasized.

In conclusion, this patient was successfully treated for toxoplasmic encephalitis with clindamycin and sulfadiazine. PCP was included in the differential diagnosis of the cavitory lung lesion. In AIDS patients who present with multiple ring-enhanced brain lesions, toxoplasmosis cannot be excluded despite an initial negative serologic test.

References

1. Dannemann B, McCutchan JA, Israelski D, et al: Treatment of toxoplasmic encephalitis in patients with AIDS: a randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfonamides. *Ann Intern Med* 1992;116:33–43.
2. Luft BJ, Remington JS: Toxoplasmic encephalitis in AIDS. *Clin Infect Dis* 1992;15:211–22.
3. Luft BJ, Remington JS: AIDS commentary. Toxoplasmic encephalitis. *J Infect Dis* 1988;157:1–6.
4. Cohn JA, McMeeking A, Cohen W, et al: Evaluation of the policy of empiric treatment of suspected *Toxoplasma* encephalitis in patients with the acquired immunodeficiency syndrome. *Am J Med* 1989;86:521–7.
5. Luft BJ, Steinberg S, Frankel R: The effect of folic and folinic acid on the anti-toxoplasma activity of pyrimethamine and sulfadiazine. In: *Program and Abstracts of the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC: American Society for Microbiology, 1988. [Abstract]
6. Haverkos HW: Assessment of therapy of *Toxoplasma* encephalitis. The TE study group. *Am J Med* 1987;82:907.
7. Brightbill TC, Post MJ, Hensley GT, et al: MR of *Toxoplasma* encephalitis: signal characteristics on T2-weighted images and pathologic correlation. *J Comput Assist Tomogr* 1996;20:417–22.
8. Porter SB, Sande MA: Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med* 1992;327:1643–8.
9. Garly ML, Petersen E, Pedersen C, et al: Toxoplasmosis in Danish AIDS patients. *Scand J Infect Dis* 1997;29:597–600.
10. Kovacs JA, Masur H: Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. *N Engl J Med* 2000;342:1416–29.
11. Ferre C, Bagueña F, Podzamczar D, et al: Lung cavitation associated with *Pneumocystis carinii* infection in the acquired immunodeficiency syndrome: a report of six cases and review of the literature. *Eur Respir J* 1994;7:134–9.