CASE REPORT

Cryptococcus dissemination triggered by steriod-pulse revealed by retrospective serum antigen study

Yoshito Takahashi

Geshi Hospital, 3-5-13 Honmachi Kochi-city 780-0870 Japan
Kochi Medical School Dept. Laboratory Medicine, Kohasu Okou-cho Nankoku-city Kochi 783-8505 Japan

Address correspondence to: Yoshito Takahashi, Geshi Hospital, 3-5-13 Honmachi kochi-city 780-0870 Japan; Telephone: +81-88-823-3257; FAX: +81-88-873-3658;
E-mail: yuutarot2@yahoo.co.jp

Running title: Cryptococcus dissemination serum antigen study
Number of text pages : 8
Number of figures: 1

Abstract

Cryptococcal meningitis developed 50 days after steroid-pulse therapy in a 76-year-old man with systemic lupus erythematosus (SLE). Retrospective serum examination revealed an apparent rise in cryptococcal antigen (CRAG) titers, starting just after the pulse therapy. The case suggests the value of screening for CRAG during steroid therapy.

Key words

cryptococcal antigen test, cryptococcal meningitis, steroid-pulse therapy, systemic lupus erythematosus

Abbreviations

SLE, systemic lupus erythematosus; CRAG, cryptococcal antigen; *C.neoformans, Cryptococcus neoformans;* CSF, cerebrospinal fluid; CT, computed tomography

Introduction

Cryptococcal meningitis is the most common clinical presentation caused by *Cryptococcus neoformans* (*C. neoformans*), a fungal pathogen, with over 1 million cases and 600,000 deaths per year worldwide [1]. Infection is believed to be acquired through the respiratory tract [2]. The majority of infection occur in the context of acquired immunodeficiency, such as AIDS or corticosteroid therapy [2]. The clinical presentation of cryptococcal meningitis is very similar in character to tuberculous meningitis, and may be fulminant in the immunosuppressed patient [3].

Report of a Case

A 76-year-old man presented with a sudden onset of staggering gait, disordered clothing and a complaint of headache, ten weeks after hospital admission for treatment of lupus pneumonitis. He had been taking 10 mg/day prednisolone (tapered from 40 mg/day on admission), and had a steroid-pulse therapy 50 days earlier (methyl-prednisolone 250 mg IV for 3 days; Figure, vertical arrow). As for immunosuppressants, he had also been taking mizoribine (50 mg/day) after the steroid-pulse therapy. He was afebrile while his headache and staggering gait continued. A cranial CT was unremarkable. On the seventh day of staggering gait, he vomited and turned febrile (37.5 centigrade). Chest radiograph and CT showed disseminated subpleural miliary lesions, reminiscent of miliary tuberculosis, and anti-tuberculosis treatment (isoniazid, rifampin and ethambutol) was started. On the twelfth day, he was comatose and cerebrospinal fluid (CSF) exam revealed numerous encapsulated yeast-like cells confirmed as *C. neoformans* by culture and enzyme immunoassay for cryptococcal antigen (CRAG; antigen titer, 2048). Treatment by a fungicide, fluconazole (200 mg/day IV) was immediately started. Three days after fluconazole treatment (on the fifteenth day), he could hold a normal conversation and was free of headache. Throughout this fifteen days (Figure, asterisk and horizontal bar), leucocyte counts, C-reactive protein, complement levels and globulin values were normal. He had positive anti-double-stranded DNA and anti-nuclear antibodies. Serum CRAG was also positive (Figure, squares). Repeated PCR tests of CSF for tuberculosis was negative and anti-tuberculosis therapy was abandoned. After one month of fluconazole therapy, CRAG titer in CSF was reduced to 128.

Serum CRAG titers were examined retrospectively, which revealed a steep rise in the titers after the steroid-pulse (Figure, diamonds with a dotted line).

Discussion

The case demonstrated an apparent rise in CRAG, suggesting dissemination of the pathogen, very likely triggered by steroid-pulse therapy which is far stronger than other immunosuppressants given concomitantly. The antigen was detectable more than a month before symptoms developed.

Although pleural fluid cultures were negative on admission, pleural effusion was refractory to prednisolone, where exists a possibility of infection, the most common cause of pulmonary infiltrates in patients with SLE [4]. Furthermore, interstitial infiltrates, as in the case, are common findings in pulmonary cryptococcosis, and also, CRAG titers are usually negative in pulmonary cryptococcosis [5]. Therefore, it is possible that pulmonary cryptococcosis was the real diagnosis.

Prognostic value of CRAG testing in HIV patient is well established, and preventive therapy before development of symptom is life-saving [6, 7]. The case suggests the life-saving value of screening for CRAG during steroid therapy. Finally, in regard of this apparent case of cryptococcal dissemination by steroid-pulses, their risks should be revisited thoroughly.

Acknowledgment

The author thank N. Matsumoto for care of the patient and discussions; honorary professors T. Sugiura and K. Hashimoto for thoughtful comments; technicians M. Morisawa, T. Morita and especially honorary chief technician S. Sugihara for serum analysis (all are members of Kochi Medical School where the case was cared and studied).

Conflict of interests

The author declare no conflict of interests.

References

1. Sloan DJ et al : Cryptococcal meningitis: epidemiology and therapeutic options. Clin Epidemiol, 6: 169-182, 2014.

2. Goldman DL et al : Persistent Cryptococcus neoformans pulmonary infection in the rat is associated with intracellular parasitism, decreased inducible nitric oxide synthase expression, and altered antibody responsiveness to cryptococcal polysaccharide. Infect Immun, 68: 832-838, 2000.

3. Gerald L Baun (ed) : Textbook of Pulmonary Diseases, 6th ed, pp590-592, Lippincott-Raven, Philadelphia, 1998.

4. Fauci AS et al : Harrison's Principle of Internal Medicine, 14th ed, p1877, McGraw-Hill, New York, 1998.

5. Aberg JA et al : Pulmonary Cryptococcosis in patients without HIV infection. Chest, 115: 734-740, 1999.

6. French N et al : Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS, 16: 1031-1038, 2002.

7. Mfinanga S et al : Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. Lancet, 385: 2173-2182, 2015.

Figure Legend

Figure. *Cryptococcus neoformans* antigen titers: Serum antigen titers increased after steroid-pulse therapy (vertical arrow). The patient was admitted on 5th April. Neurologic symptoms appeared on 8th June and remitted on 23rd June (asterisk and horizontal bar). The symptoms remitted after 3 days of fluconazole therapy. Treatments are shown under the graph. Squares with a solid line are medical exam values. Diamonds with a dotted line are retrospective study values from frozen-stored sera. Triangles indicate days with fever above 37.2 centigrade.