JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2005, p. 5828–5829 Vol. 43, No. 11
0095-1137/05/$08.00+0 doi:10.1128/JCM.43.11.5828–5829.2005

Letters to the Editor

The Role of Cryptococcal Antigen Assay in Diagnosis and Monitoring of Cryptococcal Meningitis

In a recent paper evaluating the significance of cryptococcal antigen test results for 29 Chinese human immunodeficiency virus (HIV)-negative patients affected by cryptococcal meningitis, Lu and colleagues (8) showed in all patients a decrease of antigen titer from the baseline following antifungal therapy and suggested that a decrease can be used to monitor antifungal therapy efficacy but cannot be used as an index of cure. We have reviewed our experience with 66 HIV-positive patients out of 118 with cryptococcal meningitis for whom at least three serial determinations (at baseline, day 7, and day 14) of cryptococcal antigen tests on cerebrospinal fluid (CSF) were available (1). A total of 440 determinations (range, 3 to 28 antigen determinations; median, 5 antigen determinations) were available, and for 55 patients the last determination was considered (median, 13 weeks; range, 2 to 84 weeks). In Fig. 1 is depicted the kinetics of CSF cryptococcal antigen together with the results of CSF culture. Overall, 53 patients (80%) showed a decrease of CSF antigen titer from the baseline (7 of whom had negative results), as follows: 27 cases of 1 to 3 dilutions, 16 cases of 4 to 6 dilutions, and 10 cases of 7 or more dilutions. However, 13 out of 15 of these patients for whom postmortem examination was available, despite evidence of several intravitam negative CSF cultures, still had cryptococcal meningitis or disseminated disease at autopsy (demonstrated by histopathology). Eight patients had an increase in the CSF antigen titer (four of 1 to 3 dilutions and four of 4 to 8 dilutions), and five showed stable (i.e., the same value) results throughout the follow-up. All the patients but two with an increase of CSF antigen titer had persistent positive CSF culture and died; four underwent autopsy showing disseminated cryptococcosis.

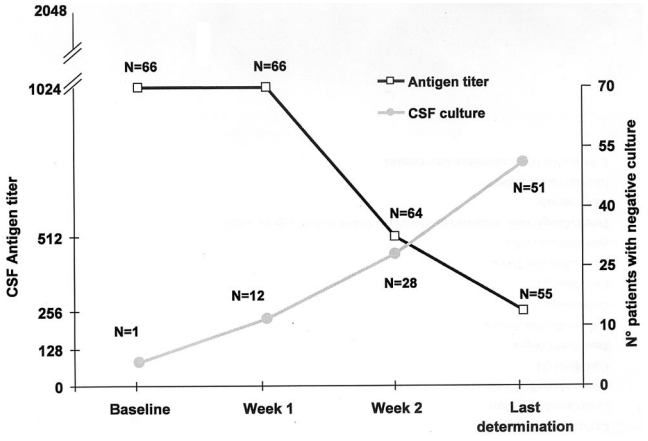

FIG. 1. Change over time of CSF cryptococcal antigen titers and correlation with CSF cryptococcal cultures in 66 HIV-positive patients. Data of CSF antigen are median values. Data regarding CSF cultures refers to the total number of patients ($n = 66$), whereas those of CSF antigen titer are the number of patients for whom it was available.

Our experience regarding the role of cryptococcal antigen to monitor antifungal therapy in AIDS patients is in keeping with that previously reported by Powderly et al. (11), who showed the lack of any correlation of changes of CSF or serum cryptococcal antigen and the outcome of cryptococcal meningitis. However, a high CSF antigen level has been identified as a sign

TABLE 1. Efficiency of different techniques in the diagnosis of cryptococcal meningitis in different hosts[a]

Reference	Country	No. of patients	Host condition	No. positive by CSF Ag (%)	No. positive by CSF culture (%)	No. positive by India ink (%)	No. positive by serum Ag (%)
12	Brazil	65	AIDS	3/3 (100)	65/65 (100)	61/65 (93.8)	NR
4	United States	89	AIDS	80/88 (90.9)	89/89 (100)	64/87 (73.5)	70/71 (98.6)
3	Australia	128	AIDS	112/128 (87.5)	111/128 (86.7)	93/128 (72.6)	NR
1	Italy	119	AIDS	112/114 (98.2)	115/118 (97.5)	84/95 (88.4)	111/112 (99.1)
Total		401		307/333 (92.2)	380/401 (94.7)	302/375 (80.5)	181/183 (98.9)
12	Brazil	44	Immunocompetent	5/6 (83.3)	26/30 (86.7)	34/44 (77.2)	NR
9	Australia	31	Immunocompetent	27/31 (87.1)	26/31 (83.5)	19/31 (61.3)	NR
3	Australia	41	Immunocompetent	40/41 (97.6)	39/41 (95.1)	36/41 (87.8)	NR
Total		116		72/78 (92.3)	91/102 (89.2)	89/116 (76.7)	181/183 (98.9)
12	Brazil	19	HIV negative, immunocompromised	NR	17/18 (94.4)	14/18 (77.8)	NR
6	United States	5	Cancer patients	5/5 (100)	5/5 (100)	5/5 (100)	NR
10	United States	157	HIV negative, immunocompromised	144/149 (96.6)	132/149 (89)	68/133 (51)	91/105 (87)
5	United States[b]	122	Organ transplant recipients	37/37 (100)	76/82 (93)	38/47 (77)	18/21 (86)
13	United States	28	Organ transplant recipients	28/28 (100)	21/28 (77)	14/28 (50)	20/22 (90.9)
Total		331		214/219 (97.7)	251/282 (89)	139/231 (60.2)	129/148 (87.2)
Overall total		848		593/630 (94.1)	722/785 (92)	430/722 (59.6)	310/331 (93.6)

[a] Ag, antigen; NR, not reported.
[b] Review of published reports.

of poor prognosis in patients with AIDS (1, 7); interestingly, more recently Thay cohorts of HIV-positive patients with cryptococcal meningitis showed a significant positive correlation between CSF cryptococcal colony-forming units (CFU) and CSF cryptococcal antigen titers at baseline ($P < 0.0001$), but the rapid rate of decline in CSF CFU was not correlated with that in CSF cryptococcal antigen titers (2).

As shown in Table 1, regardless of the different hosts in whom cryptococcal meningitis is diagnosed, among all methods employed the cryptococcal CSF antigen had the best overall sensitivity (94.1%) followed by the serum antigen (93.6%). However, some differences were observed in the different categories of hosts, with lower sensitivity in AIDS and immunocompetent patients (92%) and higher sensitivity among the other immunocompromised hosts without HIV infection. Persistently elevated CSF cryptococcal antigen in HIV-infected patients carries a poor prognosis and indicates ongoing production of viable *Cryptococcus neoformans* in tissue. In conclusion, CSF cryptococcal antigen seems to be the best test for diagnosis of cryptococcal meningitis in terms of sensitivity, but it is an unreliable tool, at least among HIV-positive patients, to drive therapeutic monitoring, particularly in assessing the point of discontinuation of antifungal therapy in HIV-infected patients.

REFERENCES

1. **Antinori, S., L. Galimberti, C. Magni, A. Casella, L. Vago, F. Mainini, M. Piazza, N. Nebuloni, M. Fasan, C. Bonaccorso, G. M. Vigevani, A. Cargnel, M. Moroni, and A. L. Ridolfo.** 2001. *Cryptococcus neoformans* infection in a cohort of Italian AIDS patients: natural history, early prognostic parameters, and autopsy findings. Eur. J. Clin. Microbiol. Infect. Dis. **20:**711–717.
2. **Brouwer, A. E., P. Teparrukkul, S. Pinpraphapora, R. A. Larsen, W. Chierakul, S. Peacock, N. Duy, N. J. White, and T. S. Harrison.** 2005. Baseline correlation and comparative kinetics of cerebrospinal fluid colony-forming unit counts and antigen titers in cryptococcal meningitis. J. Infect. Dis. **192:**681–684.
3. **Chen, S., T. Sorrell, G. Nimmo, B. Speed, B. Currie, D. Ellis, D. Marriott, T. Pfeiffer, D. Parr, K. Byth, and the Australasian Cryptococcal Study Group.** 2000. Epidemiology and host- and variety-dependent characteristics of infection due to *Cryptococcus neoformans* in Australia and New Zealand. Clin. Infect. Dis. **31:**499–508.
4. **Chuck, S. L., and M. A. Sande.** 1989. Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. N. Engl. J. Med. **321:** 794–799.
5. **Husain, S., M. M. Wagener, and N. Singh.** 2001. *Cryptococcus neoformans* infection in organ transplant recipients: variables influencing clinical characteristics and outcome. Emerg. Infect. Dis. **7:**375–381.
6. **Kontoyiannis, D. P., W. K. Peitsch, B. T. Reddy, E. E. Whimbey, X. Y. Han, G. P. Bodey, and K. V. I. Rolston.** 2001. Cryptococcosis in patients with cancer. Clin. Infect. Dis. **32:**e145–150.
7. **Larsen R. A., M. A. E. Leal, and L. S. Chan.** 1990. Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS: a randomized trial. Ann. Intern. Med. **113:**183–187.
8. **Lu, H., Y. Zhou, Y. Yin, X. Pan, and X. Weng.** 2005. Cryptococcal antigen test revisited: significance for cryptococcal meningitis therapy monitoring in a tertiary Chinese hospital. J. Clin. Microbiol. **43:**2989–2990.
9. **Mitchell, D. H., T. C. Sorrell, A. M. Allworth, C. H. Heath, A. R. McGregor, K. Papanaoum, M. J. Richards, and T. Gottlieb.** 1995. Cryptococcal disease of the CNS in immunocompetent hosts: influence of cryptococcal variety on clinical manifestations and outcome. Clin. Infect. Dis. **20:**611–616.
10. **Pappas, P. G., J. R. Perfect, G. A. Cloud, R. A. Larsen, G. A. Pankey, D. J. Lancaster, H. Henderson, C. A. Kaufmann, D. W. Hass, M. Saccente, R. J. Hamill, M. S. Holloway, R. M. Warren, and W. E. Dismukes.** 2001. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin. Infect. Dis. **33:**690–699.
11. **Powderly, W. G., G. A. Cloud, W. E. Dismukes, and M. S. Saag.** 1994. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis. Clin. Infect. Dis. **18:**789–792.
12. **Rozenbaum, R., and A. J. R. Goncalves.** 1994. Clinical epidemiological study of 171 cases of cryptococcosis. Clin. Infect. Dis. **18:**369–380.
13. **Wu, G., R. A. Vilchez, B. Eidelman, J. Fung, R. Kormos, and S. Kusne.** 2002. Cryptococcal meningitis: an analysis among 5521 consecutive organ transplant recipients. Transplant Infect. Dis. **4:**183–188.

Spinello Antinori*
Anna Radice
Laura Galimberti
Department of Clinical Sciences L. Sacco
University of Milan
Via GB Grassi 74, 20157 Milan, Italy

Carlo Magni
I Division of Infectious Diseases
L. Sacco Hospital
Milan, Italy

Marco Fasan
II Division of Infectious Diseases
L. Sacco Hospital
Milan, Italy

Carlo Parravicini
Pathology Unit
L. Sacco Hospital
Via GB Grassi 74, 20157 Milan, Italy

*Phone: 390239042668
Fax: 390250319758
E-mail: spinello.antinori@unimi.it