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An Interesting Case

Case Report

A non-immunocompromised patient with chronic meningitis and CSF leukocyte count of 256 cells/µl, glucose of 24 µg/ml and protein of 186 µg/ml has anti-*Histoplasma* antibody of 62 units but a negative *Histoplasma* antigen in the CSF.

Does this establish the diagnosis of *Histoplasma* meningitis?

Answer

No. Cross-reactivity with anti-*Histoplasma*, anti-*Coccidioides*, anti-*Blastomyces*, and anti-*Cryptococcus* antibodies necessitates establishing specific diagnosis with culture or pathology of CSF, CNS tissue, or non-CNS sites and antigen testing of CSF or non-CNS body fluids.

***Histoplasma* antigen and antibody detection in CSF are used to establish the diagnosis for CNS histoplasmosis.**

The antigen can be falsely negative while the antibody is positive in 16% of cases. The question is whether the antibody is specific for histoplasmosis. The study showed that anti-*Histoplasma* antibodies measured in the MVISTA® IgG and IgM anti-*Histoplasma* antibody EIA may cross react with anti-*Blastomyces* and anti-*Coccidioides* antibodies [1]. This patient had proven cryptococcal meningitis. Cross reactions between anti-cryptococcal and anti-*Histoplasma* antibodies have not been observed before. However, cryptococcosis and histoplasmosis have not demonstrated cross-reactivity in antigen detection assays[2-4]. A recent study identified cross reactivity to anti-*Histoplasma* antibodies does occur with anti-cryptococcal antibodies. [1]

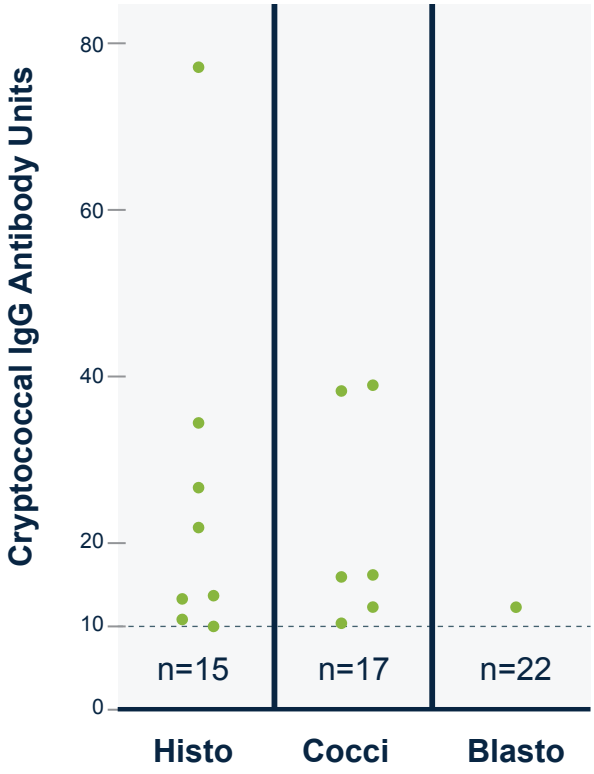
The study evaluated 61 subjects with cryptococcal meningitis including 44 with AIDS from Kampala, Uganda, 17 non-immunocompromised evaluated in a study performed at NIH, and 81 control patients. The CSF was tested for cryptococcal antibodies in an IgG anti-cryptococcal antibody EIA. CSF was tested for cross-reactivity in the IgG anti-cryptococcal antibody assay in subjects with *Histoplasma* or *Coccidioides* meningitis. Also, CSF from patients with cryptococcal meningitis and high levels of anti-cryptococcal IgG antibodies were tested for cross-reactivity in MVISTA® EIAs for anti-*Histoplasma*, anti-*Blastomyces*, and anti-*Coccidioides* IgG antibodies.

Cross reactions were seen in CSF from cryptococcal meningitis cases in the other IgG antibody EIAs, table 1. Greater cross reactivity was observed in the non-immunocompromised cohort than the AIDS cohort. Results are displayed in figure 1.

Cross reactivity in CSF from cases of cryptococcal meningitis in other MVISTA fungal antibody EIAs

IgG antibody EIA	NIH (N=13)	Kampala (N=10)	P value	Total (N=23)
Histoplasma	6 (46.2%)	2 (20.0%)	0.379	8 (34.8%)
Coccidioides	3 (23.1%)	3 (30.0%)	1.000	6 (26.1%)
Blastomyces	1 (7.7%)	0 (0%)	1.000	1 (4.3%)

NIH cohort: non-immunocompromised, Kampala: AIDS subjects



Cross reactivity in CSF from patients with other causes for fungal meningitis in the IgG anti-cryptococcal antibody EIA
10 = cutoff for positivity
n = number with negative results

Discussion: Patients with cryptococcosis with relatively intact immunity produced higher levels of IgG antibodies to *Histoplasma, Blastomyces and Coccidioides* than did those with AIDS. CSF from patients with meningitis caused by endemic mycoses also cross reacted in the IgG anti-*Cryptococcus* antibody EIA. Misdiagnosis may occur if the diagnosis is established by detection of antibodies alone. Since antigens detected in the CSF of subjects with histoplasmosis and cryptococcosis are not cross-reactive[2, 3], antigen detection, pathology, or culture are necessary to establish the correct diagnosis.

Reference List

1. Bahr, N.C., et al., *Cryptococcal meningitis is a cause for cross-reactivity in cerebrospinal fluid assays for anti-Histoplasma, anti-Coccidioides and anti-Blastomyces antibodies.* Mycoses, 2019. **62**(3): p. 268-273.
2. Bahr, N.C., et al., *Seroprevalence of histoplasmosis in Kampala, Uganda*. Med Mycol, 2016. **54**(3): p. 295-300.
3. Zhuang, D., et al., *Cryptococcal glucoxylomannan does not exhibit cross-reactivity in the MVista Histoplasma antigen enzyme immunoassay.* Clin Vaccine Immunol, 2008. **15**(2): p. 392-393.
4. Tone, K., Y. Umeda, and K. Makimura, *Cross-reactivity in Cryptococcus antigen latex agglutination test in two commercial kits*. Med Mycol, 2016. **54**(4): p. 439-43.

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