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.

<table>
<thead>
<tr>
<th>IgG antibody EIA</th>
<th>NIH (N=13)</th>
<th>Kampala (N=10)</th>
<th>P value</th>
<th>Total (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasma</td>
<td>6 (46.2%)</td>
<td>2 (20.0%)</td>
<td>0.379</td>
<td>8 (34.8%)</td>
</tr>
<tr>
<td>Coccidioides</td>
<td>3 (23.1%)</td>
<td>3 (30.0%)</td>
<td>1.000</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Blastomyces</td>
<td>1 (7.7%)</td>
<td>0 (0%)</td>
<td>1.000</td>
<td>1 (4.3%)</td>
</tr>
</tbody>
</table>

NIH cohort: non-immunocompromised, Kampala: AIDS subjects

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