Short Communication

Histoplasmosis among hospitalized febrile patients in northern Tanzania


Abstract

Histoplasmosis may be common in East Africa but the diagnosis is rarely confirmed. We report 9 (0.9%) cases of probable histoplasmosis retrospectively identified among 970 febrile inpatients studied in northern Tanzania. Median (range) age was 31 (6, 44) years, 6 (67%) were female, 6 (67%) HIV-infected; 7 (78%) were clinically diagnosed with tuberculosis or bacterial pneumonia. Histoplasmosis is an important cause of febrile illness in Tanzania but is rarely considered in the differential diagnosis. Increased clinician awareness and availability of reliable diagnostic tests may improve patient outcomes.

© 2012 Royal Society of Tropical Medicine and Hygiene. Published by Elsevier Ltd.

1. Introduction

Histoplasmosis is known to occur in sub-Saharan Africa but is rarely diagnosed. In settings with limited laboratory capacity, histoplasmosis may be difficult to distinguish from diseases with similar clinical features, such as tuberculosis and bacterial pneumonia. While Histoplasmosis capsulatum var. duboisii (H. duboisii) appears to occur more often in west Africa and Histoplasmosis capsulatum var. capsulatum (H. capsulatum) predominates in southern Africa, both varieties have been documented to cause human infection in East Africa.1

In Tanzania, H. duboisii has been isolated from environmental samples2 and H. capsulatum has been reported to cause human disease in the coastal areas around the cities of Tanga3 and Dar es Salaam,1 and has been documented in a Tanzanian expatriate.4 We report nine human cases of histoplasmosis from northern Tanzania identified by urine or serum antigen testing and highlight the challenge in clinical diagnosis of histoplasmosis in areas with limited laboratory capacity.

2. Materials and methods

From August 2007 through September 2008, we enrolled 870 febrile inpatients at Kilimanjaro Christian...
<table>
<thead>
<tr>
<th>Age, years</th>
<th>Gender</th>
<th>HIV status (CD4 count, %)</th>
<th>Urine Histoplasma antigen (ng/mL)</th>
<th>Serum Histoplasma antigen (ng/mL)</th>
<th>Mycobacterial blood culture</th>
<th>Aerobic blood culture</th>
<th>Blood parasite smear</th>
<th>Laboratory values&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Chest radiograph</th>
<th>Provisional and discharge diagnosis</th>
<th>Alive at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
<td>44</td>
<td>M</td>
<td>Infected 15, 4%</td>
<td>2.13</td>
<td>None Detected</td>
<td>Neg</td>
<td>Neg</td>
<td>WBC 3.1, HCT 34.0, Pts 257, Neut 2.5, Lym 0.4, Mono 200, Eos 279, Baso 19</td>
<td>Parenchymal abnormalities L lung alveolar infiltrates R lung multiple cavitory lesions</td>
<td>Normal Pneumonia, HIV, pulmonary TB</td>
<td>No</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td>23</td>
<td>F</td>
<td>Not infected</td>
<td>&lt;0.6</td>
<td>None Detected</td>
<td>Neg</td>
<td>Neg</td>
<td>WBC 1.6, HCT 14.8, Pts 128, Neut 0.3, Lym 1.2, Mono 112, Eos 19, Baso 11</td>
<td>Malaria, Normal</td>
<td>Anemia, malaria</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Patient 3</strong></td>
<td>31</td>
<td>F</td>
<td>Not infected</td>
<td>&gt;39.0</td>
<td>Contaminated</td>
<td>Neg</td>
<td>Neg</td>
<td>WBC 10.5, HCT 19.2, Pts 36, Neut 8.7, Lym 7.6, Mono 74, Eos 13, Baso 74</td>
<td>Nodular abnormalities micronodules throughout both lungs</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td><strong>Patient 4</strong></td>
<td>39</td>
<td>M</td>
<td>Not infected</td>
<td>&lt;0.6</td>
<td>None available for testing</td>
<td>Neg</td>
<td>Neg</td>
<td>WBC 3.0, HCT 44.3, Pts 25, Neut 1.5, Lym 0.7, Mono 777, Eos 3, Baso 4</td>
<td>Malaria, typhoid, gastroenteritis</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Patient 5</strong></td>
<td>6</td>
<td>F</td>
<td>Infected 10, 2%</td>
<td>4.01</td>
<td>None available for testing</td>
<td>Not done</td>
<td>Neg</td>
<td>WBC 16.4, HCT 29.3, Pts 379, Neut 12.1, Lym 3.2, Mono 853, Eos 131, Baso 49</td>
<td>Interstitial infiltrates probably due to Cardiomegaly</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Patient 6</strong></td>
<td>31</td>
<td>F</td>
<td>Infected 10, 2%</td>
<td>&gt;39.0</td>
<td>&gt;39.0</td>
<td>Neg</td>
<td>Neg</td>
<td>WBC 2.4, HCT 29.7, Pts 299, Neut 1.7, Lym 0.5, Mono 103, Eos 22, Baso 14</td>
<td>Nodular abnormalities Both lungs full of micronodules</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td><strong>Patient 7</strong></td>
<td>7</td>
<td>F</td>
<td>Infected 91, 6%</td>
<td>2.37</td>
<td>None available for testing</td>
<td>Not done</td>
<td>Pos Strep. pneumoniae</td>
<td>WBC 10.2, HCT 15.7, Pts 246, Neut 6.9, Lym 2.8, Mono 510, Eos 0, Baso 41</td>
<td>HIV, severe pneumonia, pulmonar TB</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Patient 8</strong></td>
<td>36</td>
<td>M</td>
<td>Infected 22, 3%</td>
<td>None available for testing</td>
<td>3.32</td>
<td>Neg</td>
<td>Neg</td>
<td>WBC 8.4, HCT 23.9, Pts 91, Neut 7.6, Lym 1.1, Mono 311, Eos 0, Baso 4</td>
<td>Normal</td>
<td>HIV, malaria, pneumonia</td>
<td>No</td>
</tr>
<tr>
<td><strong>Patient 9</strong></td>
<td>33</td>
<td>F</td>
<td>Infected 8, 1%</td>
<td>&lt;0.6</td>
<td>None available for testing</td>
<td>Neg</td>
<td>Neg</td>
<td>WBC 18.8, HCT 28.5, Pts 295, Neut 16.0, Lym 0.9, Mono 1200, Eos 508, Baso 94</td>
<td>Not done</td>
<td>HIV, pneumonias Kaposi's sarcoma, pulmonar TB</td>
<td>Yes, but died after follow up period</td>
</tr>
</tbody>
</table>

Neg: Negative; Pos.: Positive; Strep.: Streptococcus.

<sup>a</sup> Adult reference range: White blood count (WBC) 2.8–8.4*10³/μL, Hematocrit (HCT) 32–50%, Platelets (Plts) 125–445*10³/μL, Neutrophils (Neut) 0.8–5.0*10³/μL, Lymphocytes (Lym) 0.8–5.0*10³/μL, Monocytes (Mono) 56–840/μL, Eosinophilis (Eos) 0–1008/μL, Basophils (Baso) 0–84/μL.

<sup>b</sup> Pediatric reference range: (6–12 year olds) White blood count (WBC) 3.7–9.1*10³/μL, Hematocrit (HCT) 31.9–43.5, Platelets (Plts) 94–530, Neutrophils (Neut) 1.2–5.0*10³/μL, Lymphocytes (Lym) 1.6–4.7*10³/μL, Monocytes (Mono) 100–800/μL, Eosinophilis (Eos) 100–1500/μL, Basophils (Baso) 0–40/μL.
Medical Centre and Mawenzi Regional Hospital in Moshi, Tanzania, as part of a study to characterize the etiology of febrile illness. A standardized clinical history and physical examination was done by a member of the research team. Among other diagnostic samples, blood cultures, acute urine, and acute and convalescent serum were collected. After completion of study enrollment and follow-up, acute urine and serum samples that had been frozen at −80°C and transported on dry ice were tested retrospectively for Histoplasma antigen using a sandwich enzyme immunoassay (EIA) using polyclonal antibodies to H. capsulatum (the MVista Histoplasma capsulatum Quantitative Antigen EIA; Miravista Diagnostics, Indianapolis, IN, USA). Serum specimens were treated with ethylene diamine tetraacetic acid at 104°C before testing for antigen. Specimens yielding a result above the cutoff were regarded as positive. All positive results were confirmed by repeat testing. A case of probable histoplasmosis was defined as a patient with Histoplasma antigen test result from detectable <0.6 ng to >39.0. 

3. Results

Of 870 patients enrolled, 628 (72.2%) patients had urine available for Histoplasma urine antigen testing. Of these, 7 (1.1%) were found to be positive with concentrations ranging from <0.6 to >39.0 ng/mL. Of these with Histoplasma antigenuria, 4 also had serum available for testing and 2 (50%) of these also had detectable Histoplasma antigen in their serum. Of those who had urine tested an additional 200 patients (100 pediatric and 100 adult) had acute serum tested for Histoplasma antigen. From these samples 2 additional patients were found to have serum positive for Histoplasma antigen. In total, 9 (0.9%) patients met the definition of probable histoplasmosis. All results were confirmed positive on repeat testing. No patient had a positive blood culture for H. capsulatum (Table 1). Histoplasma testing was done 6–18 months after sample collection. Once available, results were provided to the clinical team.

4. Discussion

We demonstrate that Histoplasma is an etiologic agent of fever among inpatients with and without HIV infection in northern Tanzania. However, histoplasmosis was not considered in the differential diagnosis by clinicians and without the laboratory capacity to support histoplasmosis diagnosis, patients with probable histoplasmosis were often diagnosed clinically with tuberculosis, bacterial pneumonia, or malaria. The majority of patients with histoplasmosis were treated for other causes of disease based on perceptions of common etiologies for clinical syndromes. Improved awareness of the presence of histoplasmosis may lead to incorporation of the infection in differential diagnosis, particularly among persons not responding to empiric treatment for tuberculosis, community-acquired pneumonia, and malaria.

The diagnosis of histoplasmosis in this study was by antigen testing. While we collected blood cultures on all participants, blood culture techniques that would reliably detect Histoplasma fungemia were only used among adults and adolescents. In all cases Histoplasma antigen testing was reproducibly positive. The sensitivity of the Histoplasma antigen test among HIV-infected patients is 100% in urine and 92.3% in serum, and the specificity of both is 99% among controls. Detection of antigen is a basis for a probable diagnosis of histoplasmosis in patients with compatible clinical findings. While it is uncertain whether our patients had H. capsulatum or H. duboisii, as the antigen detected in both mycoses is cross reactive, clinical features and other case series done in East Africa suggest that H. capsulatum is likely to predominate.

Although Histoplasma has been isolated from patient samples in Tanzania in the past, none of the patients reported in our series had positive fungal cultures. Consequently, the diagnosis of probable histoplasmosis relied on the combination of antigen detection and clinical features. Future research should focus on identifying culture-confirmed histoplasmosis to allow validation of non-culture diagnostic techniques in the sub-Saharan Africa setting. Adaptation and validation of Histoplasma antigen tests for use in low resource settings could assist with recognition of patients with the infection.

In conclusion, histoplasmosis is a cause of fever among inpatients in northern Tanzania but is rarely considered by clinicians in settings with limited laboratory capacity. Patients with histoplasmosis often receive a clinical diagnosis of tuberculosis, bacterial pneumonia or malaria leading to inappropriate treatment. Improved access to diagnostic tests for histoplasmosis, including the development of an appropriately validated simple Histoplasma antigen test suitable for use in low- and middle-income countries where histoplasmosis is endemic may improve patient outcomes.

Authors’ contributions: JAC, ABM, and LJW conceived the work; VPM, LJM, GDK, WS, and HOR were responsible for the clinical data collection; HCD read chest radiographs; ABM coordinated processing, archiving, and shipping of laboratory samples; EJK and LJW conducted and interpreted Histoplasma laboratory work; SML compiled and analyzed data and wrote the first draft of the manuscript. All authors contributed to the revision of the manuscript and read and approved the final version. SML and JAC are guarantors of the paper.

Acknowledgements: The authors thank Ahaz T. Kulanga, MBA, for providing administrative support to this study and Pilli M. Chambo, Beata V. Kyara, Beatus A. Massawe, Anna D. Mtei, Godfrey S. Mushii, Lillian E. Ngowi, Boniface N. Njau, Flora M. Nkya, and Winfrida H. Shirima for interviewing and enrolling study participants. We are grateful to the leadership, clinicians and patients of KCMC and MRH for their contributions to this research. We thank Miravista Diagnostics, Indianapolis, Indiana, USA, for performing Histoplasma capsulatum Quantitative Antigen EIA on patient samples. We acknowledge the Hubert-Yeargan Center for Global Health at Duke University for critical infrastructure support for the Kilimanjaro Christian Medical Centre-Duke University Collaboration.
Funding: This research was supported by an International Studies on AIDS Associated Co-infections (ISAAC) award, a United States National Institutes of Health (NIH) funded program (U01 AI062563). Authors received support from NIH awards ISAAC (ABM, VPM, LJM, GDK, HOR, JAC); AIDS International Training and Research Program D43 PA-03-018 (ABM, VPM, HOR, JAC); the Duke Clinical Trials Unit and Clinical Research Sites U01 AI069484 (VPM, JAC), the Duke Center for AIDS Research (Duke U01 AI 64518 (L-YY, S-CC); the Center for HIV/AIDS Vaccine Immunology U01 AI067854 (JAC); and the Hubert-Yeargan Center for Global Health at Duke University (SML).

Competing interests: L. Joseph Wheat is Director and Emily J. Kirsch is an employee of Miravista Diagnostics.

Ethical approval: This study was approved by the KCMC Research Ethics Committee, the Tanzania National Institutes for Medical Research National Research Ethics Coordinating Committee, and an Institutional Review Board of Duke University Medical Center.

References