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Histoplasmosis among hospitalized febrile patients in northern Tanzania

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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 (66.7%) were female, 6 (66.7%) HIV-infected; 7 (77.8%) 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.

Keywords

Africa; Histoplasmosis; HIV; Tanzania; Tuberculosis

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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.

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

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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 samples[2] and *H. capsulatum* has been reported to cause human disease in the coastal areas around the cities of Tanga[3] 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 Medical Centre and Mawenzi Regional Hospital in Moshi, Tanzania, as part of a study to characterize the etiology of febrile illness.[5,6] 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.[7] Specimens yielding a result above the cutoff were regarded as positive.[8,9] 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.[9]

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%) [V1]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.[5,6] 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 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[10] 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.[7,9] Detection of antigen is a basis for a probable diagnosis of histoplasmosis in patients with compatible clinical findings.[11] While it is uncertain whether our patients had *H. capsulatum* or *H. duboisii,* as the antigen detected in both mycoses is cross reactive,[12] clinical features and environmental surveys and other case series done in East Africa suggest that *H. capsulatum* is likely to predominate.[3]

Although *Histoplasma* has been isolated from patient samples in Tanzania in the past,[13] 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.[14]

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.

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Table 1

Characteristics and laboratory findings, patients with positive urine and serum *Histoplasma* antigen, northern Tanzania, 2007–8

	Age, years	Gender	HIV status (CD4 if pos)	Urine Histoplasma antigen (ng/mL)	Serum Histoplasma antigen (ng/mL)	Mycobacterial blood culture	Aerobic blood culture	Blood parasite smear	Laboratory values[a,b]	Chest radiograph	Provisional and discharge diagnosis	Alive at follow-up
Patient 1	44	M	Infected CD4 15, 4%	2.13	None Detected	Neg	Neg	Neg	WBC 3.1, HCT 34.0, Plts 257, Neut 2.5, Lym 0.4, Mono 200, Eos 279, Baso 19	Parenchymal abnormalities L lung alveolar infiltrates R lung multiple cavitary lesions	Pneumonia, HIV, pulmonary TB	No
Patient 2	23	F	Not infected	<0.6	None Detected	Neg	Neg	Neg	WBC 1.6, HCT 14.8, Plts 128, Neut 0.3, Lym 1.2, Mono 112, Eos 19, Baso 11	Normal	Anemia, malaria	Yes
Patient 3	31	F	Not infected	>39.0	>39.0	Contaminated	Neg	Neg	WBC 10.5, HCT 19.2, Plts 36, Neut 8.7, Lym 7.6, Mono 74, Eos 13, Baso 74	Nodular abnormalities micronodules throughout both lungs	HIV, pneumonia, malaria, gastroenteritis	Yes
Patient 4	39	M	Not infected	<0.6	None available for testing	Neg	Neg	Neg	WBC 3.0, HCT 44.3, Plts 25, Neut 1.5, Lym 0.7, Mono 777, Eos 3, Baso 4	Not done	Malaria, typhoid, gastroenteritis	Yes
Patient 5	6	F	Infected CD4 10, 2%	4.01	None available for testing	Not done	Neg	Neg	WBC 16.4, HCT 29.3, Plts 379, Neut 12.1, Lym 3.2, Mono 853, Eos 131, Baso 49	Interstitial infiltrates probably due to edema Cardiomegaly	Congestive cardiac failure, mitral regurgitation, severe pneumonia	Yes
Patient 6	31	F	Infected CD4 10, 2%	>39.0	>39.0	Neg	Neg	Neg	WBC 2.4, HCT 29.7, Plts 299, Neut 1.7, Lym 0.5, Mono 103, Eos 22, Baso 14	Nodular abnormalities Both lungs full of micronodules	HIV, oral candidiasis, pulmonary TB	Yes
Patient 7	7	F	Infected 91, 6%	2.37	None available for testing	Not done	Pos *Strep. pneumoniae*	Neg	WBC 10.2, HCT 15.7, Plts 246, Neut 6.9, Lym 2.8, Mono 510, Eos 0, Baso 41	Not done	HIV, severe pneumonia, pulmonary TB	Yes
Patient 8	36	M	Infected 22, 3%	None available for	3.32	Neg	Neg	Neg	WBC 8.4, HCT 23.9, Plts 91, Neut 7.0, Lym 1.1, Mono 311, Eos 0, Baso 4	Normal	HIV, malaria, pneumonia	No
Patient 9	33	F	Infected 8, 1%	None available for testing	<0.6	Neg	Neg	Neg	WBC 18.8, HCT 28.5, Plts 395, Neut 16.0, Lym 0.9, Mono 1200, Eos 508, Baso 94	Not done	HIV, pneumonia, Kaposi's sarcoma, pulmonary TB	Yes, but died after follow

Age, years	Gender	HIV status (CD4 if pos)	Urine Histoplasma antigen (ng/mL)	Serum Histoplasma antigen (ng/mL)	Mycobacterial blood culture	Aerobic blood culture	Blood parasite smear	Laboratory values[a,b]	Chest radiograph	Provisional and discharge diagnosis	Alive at follow-up
											up period

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

[a]Adult range: White blood count (WBC) 2.8–8.4*10^3/uL, Hematocrit (HCT) 32–50%, Platelets (Plts) 125–445*10^3/uL, Neutrophils (Neut) 0.8–5.0*10^3/uL, Lymphocytes (Lym) 0.8–5.0*10^3/uL, Monocytes (Mono) 56–840/uL, Eosinophils (Eos) 0–1008/uL, Basophils (Baso) 0–84/uL

[b]Pediatric range: (6–12 year olds) White blood count (WBC) 3.7–9.1*10^3/uL, Hematocrit (HCT) 31.9–43.5, Platelets (Plts) 94–530, Neutrophils (Neut) 1.2–5.0*10^3/uL, Lymphocytes (Lym) 1.6–4.7*103/uL, Monocytes (Mono) 100–800/uL, Eosinophilias (Eos) 100– 1500/uL, Basophils (Baso) 0–40/uL[15]