Histoplasmosis in a Non-Endemic Area: An Often Unrecognized Disease

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ABSTRACT

Background:
In non-endemic regions, providers are often unfamiliar with the protean manifestations of histoplasmosis. Consequently, the disease may be overlooked, leading to delays in diagnosis. As pockets of previously unrecognized endemicity are identified and an increasing number of people migrate from high-prevalence areas, it becomes imperative to better characterize histoplasmosis in a non-endemic region.

Methods:
We performed a retrospective chart review of microbiologically or histopathologically-confirmed cases of histoplasmosis at Yale New Haven Hospital in Connecticut from 2005 to 2015. Active histoplasmosis was defined as symptomatic disease.

Results:
A total of 20 patients were identified. An incidental diagnosis was made in 8 patients after biopsy of asymptomatic pulmonary nodules, most commonly as part of malignancy screening (n=4). Among 12 patients with active histoplasmosis, the mean age was 54 years, 10 were male, 6 were Hispanic and 7 were immunosuppressed (HIV/AIDS =5, HSCT=1, SOT=1). Eleven patients reported travel to endemic areas (Caribbean in 6). Constitutional symptoms were present in 6. Five patients were admitted to the ICU and 2 developed ARDS. Disseminated histoplasmosis was diagnosed in 8 cases. The most common extra-pulmonary sites were the oral mucosa (n=3) and bone marrow (n=3). Histopathology and culture were positive in 11 and 5 cases, respectively. Urine *Histoplasma* antigen was positive in 6 patients. Eight patients received amphotericin B.

Median time to diagnosis from symptom onset and initial evaluation were 41 days (15-226) and 28 days (4-106), respectively. Median time to first *Histoplasma* antigen testing was 29 days (2-114). Extensive workup (≥5 imaging or invasive procedures) was performed in 9 patients while 6 were either discharged or died without diagnosis. Treatment success was achieved in 8 patients; 2 failed treatment and 2 died.

Conclusion:
In this Connecticut series of histoplasmosis cases, immunosuppression, particularly HIV/AIDS, and travel to the Caribbean were notable risk factors. Failure to recognize the disease may contribute to delayed diagnosis, extensive testing and worse outcomes. Histoplasmosis should be considered in patients presenting with compatible signs and symptoms in a non-endemic area.

METHODS

- We performed a retrospective chart review of microbiologically or histopathologically-confirmed cases of histoplasmosis at Yale New Haven Hospital in Connecticut from 2005 to 2015.
- Active histoplasmosis was defined as the following: 1) presence of clinical disease and 2) fulfillment of the microbiologic or histopathologic criteria of the EORTC-MSG for proven, endemic fungal infection.
- The search strategy included: (1) Pathology records for histopathologic evidence of histoplasmosis, (2) Clinician referred cases, (3) Microbiology records for cultures positive for *H.capsulatum* and (4) Electronic medical records using ICD-9 codes for histoplasmosis
- After duplicates were eliminated, 12 cases of proven active histoplasmosis were found
- Treatment failure was defined as clinical, radiographic or microbiologic evidence of disease progression while on adequate therapy, leading to death, clinical worsening or relapse

RESULTS

Table 1. Baseline characteristics of patients with active histoplasmosis

Characteristic	N = 12 (%)
Age (Median ± Standard Deviation) (years)	54 ± 16
Sex	
Male	10 (83)
Female	2 (17)
Race	
Hispanic	6 (50)
White	4 (33)
Black	1 (8)
Asian	1 (8)
Underlying conditions	10 (83)
Chronic conditions	4 (33)
Solid organ malignancy	3 (25)
Diabetes mellitus	2 (17)
Cirrhosis	1 (8)
Immunosuppressive conditions	8 (67)
HIV	5 (42)
AIDS (with CD4 <100)	4 (33)
Hematopoietic Stem Cell	1 (8)
Transplant	1 (8)
Solid organ transplant	1 (8)
Systemic Lupus Erythematosis	
Charlson Comorbidity Score (median ± SD)	6 ± 3
Exposure history	4 (33)
Landscaping/soil exposure	3 (25)
Waterway exposure	1 (8)
Travel to endemic areas	11(92)
Caribbean/Latin America	6 (50)
Puerto Rico	5 (42)
Guatemala	1 (8)
Midwest	3 (25)
East Coast (North Carolina)	2 (17)
Southwest	2 (17)
South-East Asia	1 (8)

Table 2. Clinical characteristics of patients with active histoplasmosis

Characteristic	N = 12 (%)
Clinical presentation	
Constitutional symptoms	6 (50)
Fever	5 (42)
Fatigue	3 (25)
Weight loss	3 (25)
Night sweats	1 (8)
Oral lesions	3 (25)
Respiratory symptoms	3 (25)
Cough	2 (17)
Pleuritis	1 (8)
Respiratory failure	1 (8)
Cutaneous lesions	2 (17)
Papular Rash	2 (17)
Ulcer	1 (8)
Acute mental status change	2 (17)
Gastrointestinal symptoms	2 (17)
Diarrhea	1 (8)
Hematochezia	1 (8)
Generalized edema	2 (17)
Laboratory abnormalities	
Liver function test abnormalities	7 (58)
Anemia (Hb<12)	6 (50)
LDH> 200	6 (50)
Abnormal WBC	4 (33)
Leukopenia	3 (25)
Leukocytosis	1 (8)
Hyponatremia	4 (33)
Radiology findings	
Lung nodules	10 (83)
Splenomegaly	2 (17)
Liver lesions	2 (17)
Adrenal mass	1 (8)
Bone or Soft tissue abnormalities	1 (8)
Brain lesions	1 (8)
Gastrointestinal lesions	1 (8)

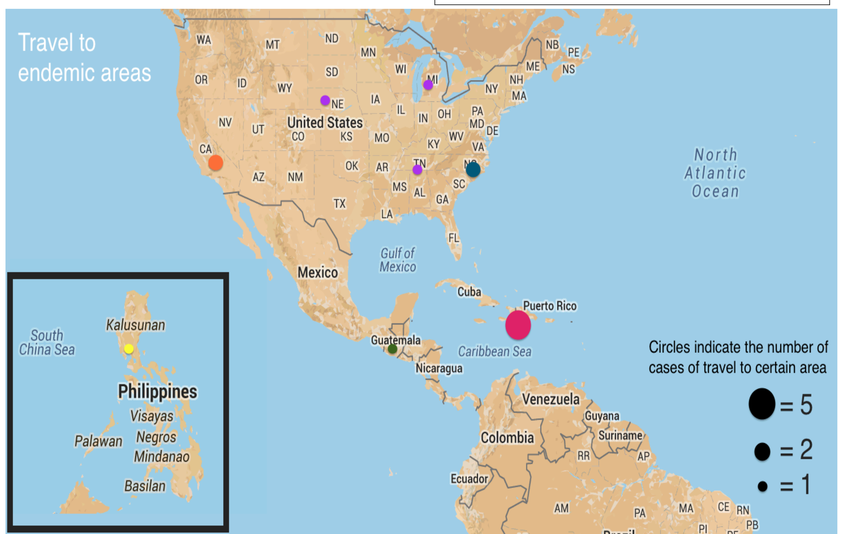

Table 3. Disease extent, severity and diagnostics of patients with active histoplasmosis

Characteristic	N = 12 (%)
Extent of disease	
Pulmonary	4 (33)
Disseminated	8 (67)
Extrapulmonary location	
Oral mucosa	3 (25)
Bone marrow	3 (25)
Blood	2 (17)
Spleen	2 (17)
Liver	2 (17)
Skin	2 (17)
Adrenal glands	1 (8)
Bone	1 (8)
CNS	1 (8)
Colon	1 (8)
Acute Respiratory Distress Syndrome	2 (17)
Highest level of care	
Outpatient	3 (25)
Inpatient	4 (33)
Intensive Care Unit	5 (42)
Source of diagnosis	
Lung/Mediastinal tissue biopsy	4 (33)
Blood culture	2 (17)
Bone marrow biopsy	2 (17)
Bronchoalveolar lavage	2 (17)
Bone/Soft tissue biopsy	1 (8)
Oral ulcer biopsy	1 (8)
Colonic biopsy	1 (8)
Adrenal biopsy	1 (8)
Lymph node biopsy	1 (8)
Positive culture	5 (42)
Tissue	3 (25)
Blood	2 (17)
Cerebrospinal fluid	0 (0)
Positive histopathology	9 (75)
Positive cytology	2 (17)
Histoplasma Antigen (Ag)	6/11 (55)
Urine Ag	6/11 (55)
Blood Ag	1/1 (100)
Cerebrospinal fluid Ag	1/1 (100)

Table 4. Treatment and outcomes for patients with active histoplasmosis

Characteristic	N = 12 (%)
Amphotericin B use	8 (67)
Liposomal AMB	5 (42)
Conventional AMB	3 (25)
Duration (median ± SD)	2.5 ± 4
Azole use	10 (83)
Itraconazole	9 (75)
Voriconazole	1 (8)
Clinical outcome	
Improvement	8 (67)
Treatment Failure	
Death	2* (17)
Worsening	1 (8)
Relapse	1 (8)
Duration of follow-up (median ± SD) (months)	2.5 ± 6

*Attributable to histoplasmosis

Table 5. Time to diagnosis of patients with active histoplasmosis

Characteristic	N = 12 (%)
Time to diagnosis (median ± SD) (days)	41 ± 75
From symptom onset	28 ± 30
From initial evaluation	
Time to Histoplasma antigen testing (median ± SD) (days)	29 ± 35
Delay in diagnosis (≥14 days from admission)	7 (58)
Extensive workup (≥5 imaging modalities and/or invasive procedures)	9 (75)
Discharged at least once or death without diagnosis	6 (50)

CONCLUSION

- In this Connecticut series, we noted a high prevalence of immunosuppression, particularly HIV/AIDS, and travel to the Caribbean
- Delays in diagnosis and extensive testing were seen in the majority of cases
- Histoplasmosis should be considered in patients presenting with compatible signs and symptoms in a non-endemic area
- Enhanced awareness of the disease in non-endemic areas may contribute to more rapid diagnosis of this potentially fatal mycosis