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Major Article

Predictive factors for disseminated histoplasmosis in AIDS patients with fever admitted to a reference hospital in Brazil

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Abstract

Introduction: In many settings, the lack of sensitive biomarkers of disseminated histoplasmosis (DH) leads to a clinical reliance on older diagnostic methods and delayed treatment initiation. The early recognition of DH is critical for survival, especially in patients with human immunodeficiency virus (HIV). This study aimed to identify clinical and laboratory findings associated with the definitive diagnosis of DH in low-income HIV patients in endemic areas. **Methods:** Febrile AIDS patients with suspected DH who were admitted to a reference hospital in northeastern Brazil from January 2006 to January 2007 were evaluated for clinical and laboratory findings associated with DH diagnosis. **Results:** One hundred seventeen patients with fever were included, and 48 (41%) cases of DH were determined by *Histoplasma capsulatum* identification. A higher fever (≥38.5ºC), maculopapular/papular rash, splenomegaly, hepatomegaly, wheezing, hemoglobin ≤9.5g/dL, platelets ≤80,000/µL, CD4 count ≤75/µL, aspartate aminotransferase (AST) level ≥2.5 times the upper limit of normal (ULN), lactate dehydrogenase (LDH) ≥5times the ULN; and international normalized ratio (*INR) >2* times the ULN were significantly associated with DH. A multivariable analysis identified hepatomegaly [adjusted (a) prevalence ratio (PR)= 1.96; 95% confidence interval (CI): 1.21-3.16), CD4 count ≤75/µL (aPR = 2.02; 95% CI: 1.06–3.83), LDH ≥5 times the ULN (aPR = 2.23; 95% CI: 1.44-3.48), and maculopapular/papular rash (aPR = 1.70; 95% CI: 1.02-2.83) were independent risk factors for DH. **Conclusions:** These easily assessed parameters can facilitate clinical decision-making for febrile AIDS patients with suspected DH in low socioeconomic and *Histoplasma*-endemic regions.

Keywords: *Histoplasma*. Diagnosis. AIDS. HIV.

INTRODUCTION

Disseminated histoplasmosis (DH) is a severe systemic mycosis caused by *Histoplasma capsulatum* that occurs mainly in immunocompromised individuals, particularly HIV patients[1,2] with cluster of differentiation *4* (CD4) counts <200 cells/mm^3.

In recent decades, a large number of DH cases have been observed in Ceará State, Northeast Brazil[3,4]. In a study conducted from January 2006 to December 2010 at a reference hospital in Ceará, 208 cases of DH and acquired immunodeficiency syndrome (AIDS) were identified, with a case fatality rate of 42.3%[5].

The diagnosis of histoplasmosis, especially the disseminated form, presents a clinical challenge. Additionally, access to diagnostic tests and effective treatment varies widely, depending on the country in which the patient resides[2]. In the United States, the identification of *Histoplasma* antigen in urine or blood samples (Mira Vista Laboratory, Indianapolis, IN, USA; 97% sensitivity, 85% specificity) is the most used test for detecting disseminated histoplasmosis/human immunodeficiency virus (DH/HIV) co-infection[6]. This test accelerates case resolution and reduces mortality.

In contrast, in countries with low and middle socioeconomic statuses, the diagnosis and treatment of DH are often delayed, with subsequently high rates of mortality[3,5]. This situation is a consequence of the limited availability of advanced diagnostic methods for *H. capsulatum* infection, together with the increased incidence of diseases with similar symptoms (e.g., tuberculosis and visceral leishmaniasis), which contribute to misdiagnosis and the administration of multiple associated treatments[7]. In such settings, diagnostic approaches rely on slow and/or poorly sensitive methods such as fungal culture and the staining of smears[3-5,8].

The presumptive diagnosis of DH is an important tool for case management in areas with few resources. Such diagnoses are usually based on clinical and laboratory findings associated with the disease, such as fever, malaise, cough, weight loss, hepatomegaly, skin/mucosal involvement, pancytopenia, and increases in the levels of lactate dehydrogenase (LDH),

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aspartate aminotransferase (AST), and ferritin[5,8-10]. Although DH is well known, no systematic Brazilian studies have evaluated the diagnostic accuracies of these parameters alone or in combination.

Given the difficulties associated with the diagnosis of DH in low-income countries and the effects of early treatment on the prognosis of this illness, we conducted a study to identify the signs, symptoms, and laboratory parameters associated with the diagnosis of DH in febrile AIDS patients with a presumptive diagnosis of DH who were admitted to Hospital São José, a reference health facility for HIV in the State of Ceará, Brazil.

METHODS

Study population and inclusion criteria

A prospective study was conducted at *Hospital São José,* a public reference hospital for infectious diseases responsible for the care of 83% of HIV-positive patients residing in Ceará State, Northeast Brazil (total population: 8.8 million inhabitants). An AIDS diagnosis was made according to the 1987 AIDS case definition of the Centers for Disease Control and Prevention[1].

From January 2006 to January 2007, hospitalized AIDS patients aged >18 years who fulfilled the following criteria upon admission were considered eligible for the study: fever (body temperature >37.8°C) and elevated LDH level or leukopenia; thrombocytopenia; and at least one of the following conditions: respiratory disease (cough and dyspnea), diarrhea, hepatomegaly, splenomegaly, enlarged lymph nodes or mucocutaneous manifestations (generalized papular eruption, throat or skin ulcers, scaly or infiltrative plaques, nodules or other atypical manifestation). All included patients were evaluated in the same manner. A systematic search for fungal elements on stained smear and culture of buffy coat was performed for every patient. If present, skin/mucosal lesions were also biopsied and processed for fungus as described above, as well as for histopathology. Bone marrow and other tissues were investigated for fungus at the request of the attending physician.

DH cases were confirmed by *H. capsulatum* identification in clinical specimens other than lung tissue. Non-DH patients included those who had negative *H. capsulatum* cytology and culture from body tissues and another diagnosis established at discharge or at death and who were found not to have developed DH after a review of the medical records latterly after discharge. Patients with a negative fungal culture who exhibited clinical improvement with antifungal treatment and those who died or were discharged before clinical and laboratory evaluations were completed were excluded.

Study design

The same trained personnel visited the clinical wards thrice weekly for study recruitment and data collection. A pretested structured questionnaire was used to collect sociodemographic, clinical, and laboratory data at hospital admission. CD4 counts were considered valid when collected 3 months prior to admission for patients with previously diagnosed AIDS or up to 3 months after admission for those in whom HIV was detected during hospitalization. A careful review of the patients' records was conducted 6-12 months after study recruitment to collect culture results and information regarding the patients' clinical situations, final diagnoses, and mortality outcomes.

Statistical analysis

Epi-Info, version 6.04d (Centers for Disease Control and Prevention, Atlanta, GA, USA) was used for data entry. The Kruskal-Wallis test was used to compare numeric variables. Associations of the presence of DH with the investigated epidemiological variables were analyzed using contingency tables with prevalence ratios and 95% confidence intervals (CI). We selected variables that were identified as clinically relevant in previous studies and/or statistically significant in the current bivariate analysis; these were grouped into three blocks– sociodemographic, clinical, and laboratory – for the multivariable analysis. We used a generalized linear model (GLM) and Stata version 15 (Stata Corporation, College Station, TX, USA) with a logarithmic link and the Poisson distribution family to estimate the prevalence ratios and confidence intervals, and applied robust error variances to evaluate the differences between the categories of explanatory variables with respect to the outcome in the final model[11]. The regression analysis was conducted separately for the clinical and laboratory blocks; in a second step, the variables that remained in both models were analyzed together in a final regression model.

Ethical considerations

This study was approved by the Ethical Review Board of São José Hospital of Infectious Diseases, Fortaleza, Brazil.

RESULTS

A total of 165 AIDS patients with a presumptive diagnosis of DH were identified. Forty-eight patients were excluded because a fungal culture was not performed (n = 29), empirical treatment with amphotericin B elicited a response despite a negative fungal culture (n = 15), or no diagnosis was established at discharge (n = 4); the remaining 117 (70.9%) subjects were included in the data analysis.

H. capsulatum was identified in 48 (41%) of the 117 cases. DH was the AIDS-defining disease in 26 (54.1%) of these 48 cases and in two patients (4.1%) a previous episode of this mycosis was recorded. In 69 (58.9%) of 117 patients, the fungal culture was negative, another diagnosis was established at discharge or death, and DH had not developed at the time of the final medical record review (6-12 months after study recruitment).

The diagnosis of DH was established from stained smears in 31 (64.5%) of 48 cases, by culture in 15 (31.2%) cases, and by histopathology of the skin in two (4.1%) cases. Twenty-three (74.1%) patients with positive smears also had positive fungal cultures. Six (12.5%) patients with DH were diagnosed by positive culture after discharge. Of these, four exhibited clinical improvements after intravenous therapy with sulfamethoxazole-trimethoprim during hospitalization and were discharged; however, three were readmitted 1-3 months later because

of clinical exacerbation for which they received treatment with amphotericin B. The other two patients diagnosed after discharge died before treatment initiation. Overall, 10 (20.8%) patients with DH died during hospitalization.

The time to death from hospital admission did not differ between the two groups. These median times were 19.5 days [interquartile range (IQR) = 7-23] among DH patients and 21.5 days (IQR = 13-33) among non-DH patients ($p = 0.30$).

The most frequent diagnoses of patients without DH were tuberculosis (n = 17/69; 24.6%) identified via smear microscopy, culture, or clinicoradiologic criteria according to the 2004 Brazilian Ministry of Health guideline[12]; bacterial pneumonia (n = 11; 16%); cerebral toxoplasmosis (n = 10; 14.5%); chronic diarrhea (n = 6; 8.7%); pneumocystis pneumonia (n = 4; 5.8%); Kala-azar (n = 4; 5.8%); and bacterial sepsis (n = 4; 5.8%). Other illnesses included esophageal candidiasis (n =2) and neurocriptococosis, abdominal pain, pharmacodermia, hepatitis, herpes simples, hepatic insufficiency, chronic renal failure, leukopenia to drugs, peripherical neuropathy, pancreatitis, and Kaposi sarcoma (n = 1 each). Fourteen (20.2%) non-DH patients died during hospitalization.

Socio-demographic characteristics

The sociodemographic factors are presented in **Table 1**. The only statistically significant difference among the patients was the place of birth ($p = 0.02$).

Clinical and laboratory parameters

The most common signs and symptoms in the DH group, besides fever (inclusion criterion), were weight loss (n = 48; 100%), anorexia (n = 40/48; 83.3%), malaise (n = 39/48; 81.2%), chills (n = 23/30; 76.7 %), cough (n = 34/48; 70.8%), daily fever (n = 33/47; 70.2%), vomiting (n = 25/48; 52.1%), and diarrhea (n = 25/48; 52%).

DH occurred >3 times more frequently in patients with body temperatures ≥38.5ºC. The other clinical findings that associated significantly with DH are listed in **Table 2**. Pleuritic chest pain was more common in non-DH patients (**Table 2**).

Eighteen patients with DH (35.5%) presented with mucocutaneous lesions that improved with amphotericin B treatment. In 14 cases, histoplasmosis was confirmed by histopathology; two patients refused a biopsy and the remaining two had already been diagnosed with DH and had platelet counts too low to conduct invasive procedures.

Patients with and without DH did not differ significantly with respect to median body weight (52.5 *vs* 52.0kg; $p = 0.65$), systolic blood pressure (100mmHg for both), pulse rate (102 *vs* 88 bpm; $p = 0.11$), and respiratory rate (20.5 *vs* 20 breaths/min, $p = 0.85$).

The laboratory test parameters found to associate significantly with DH are listed in **Table 2**. Patients with DH had a significantly lower median CD4 count, compared to those without DH (24 *vs* 96 cells/μL; $p < 0.01$). However, this group had significantly higher median LDH (1,882 *vs* 622.5 IU/L; $p < 0.01$), AST (113.5 *vs* 40IU/L; $p < 0.01$), and alanine aminotransferase levels (ALT; 51.1 *vs* 30.1IU/L; $p < 0.01$).

Logistic regression analysis

A logistic regression analysis identified hepatomegaly, a CD4 count ≤75 cells/μL, LDH level ≥5x the upper limit of normal (UNL), and a maculopapular or papular rash as independent risk factors for DH (**Table 3**).

TABLE 1: Socio-demographic factors associated with the diagnosis of disseminated histoplasmosis in AIDS patients in Brazil, 2006-2007.

Variable	DH n (%)	Prevalence ratio (95% CI)
Age (years)		
18–30	18/39 (46.2)	1.34 (0.74–2.35)
31–40	17/40 (42.5)	1.24 (0.70–2.19)
41–62	13/38 (34.2)	Reference
Sex		
male	40/95 (42.1)	1.15 (0.63–2.11)
female	8/22 (36.4)	Reference
Education (years)		
illiterate	7/11 (63.6)	1.77 (1.02–3.08)
1–7	23/64 (35.9)	Reference
8–12	12/27 (44.4)	1.23 (0.72–2.10)
>12	3/8 (37.5)	1.04 (0.40–2.70)
Place of birth		
capital	27/51 (52.9)	Reference
rural areas	17/55 (30.9)	0.58 (0.36–0.93)
other localities	4/11 (36,4)	0.68 (0.30–1.56)
Monthly family income		
<1 mw*	10/25 (40.0)	0.76 (0.42–1.38)
1–3	31/82 (37.8)	Reference
>3	4/7 (57.1)	1.51 (0.75–3.04)

AIDS: acquired immunodeficiency syndrome; **DH**: disseminated histoplasmosis; **95% CI:** 95% confidence interval. *Minimum wage (US$ 223.00, January 2006).

TABLE 2: Signs, symptoms, and laboratory findings associated with the diagnosis of disseminated histoplasmosis in AIDS patients in Brazil, 2006-2007.

Sign/symptom (DH/total patients)	**DH**	**Prevalence ratio**
	n (%)	**(95% CI)**
Temperature ≥38.5°C (48/114)	44/88 (50.0)	3.25 (1.28–8.20)
Daily fever (47/113)	33/76 (43.4)	1.14 (0.70–1.86)
Chills (30/71)	23/55 (41.8)	0.95 (0.50–1.80)
Rash* (48/117)	15/17 (88.2)	2.67 (1.92–3.71)
Splenomegaly (48/117)	16/25 (61.5)	1.84 (1.22–2.76)
Hepatomegaly (48/117)	31/57 (54.4)	1.91(1.20–3.06)
Lymph nodes** (48/117)	20/47 (42.5)	1.06 (0.68–1.65)
Anorexia (48/117)	40/94 (42.5)	1.22 (0.66–2.24)
Wheezing (46/114)	8/10 (80.0)	2.18 (1.47–3.26)
Arthralgia (48/117)	10/36 (27.7)	0.59 (0.33–1.05)
Cough (48/117)	34/82 (41.5)	1.03 (0.64–1.67)
Pleuritic pain (48/117)	4/26 (15.3)	0.31 (0.12–0.80)
Hg ≤9.5g/dl (48/117)	31/62 (50.0)	1.62 (1.01–2.58)
Leuk ≤4,000/µL (48/117)	27/59 (45.8)	1.26 (0.81–1.96)
Plts ≤80,000/µL (48/116)	14/23 (60.8)	1.66 (1.09–2.54)
CD4 ≤75 cells/µL (35/85)	27/49 (55.1)	2.47 (1.28–4.80)
AST ≥2.5x ULN (44/105)	24/31 (77.4)	2.86 (1.88–4.36)
ALT ≥2.5x ULN (42/104)	6/10 (60.0)	1.56 (0.88–2.76)
INR ≥2.0 (32/117)	9/14 (64.3)	1.70 (1.07–2.69)
LDH ≥5x ULN (46/114)	19/23 (82.6)	2.78 (1.92–4.02)
Urea ≥2x ULN (43/107)	2/7 (28.6)	0.70 (0.21–2.30)
Cr ≥2x ULN (46/113)	4/8 (50.0)	1.25 (0.60–2.60)
Albu <3.5g/dL (48/116)	32/66 (48.5)	1.51 (0.94–2.43)

AIDS: acquired immunodeficiency, syndrome; **DH**: disseminated histoplasmosis; **95% CI:** 95% confidence interval; **Hg:** hemoglobin; **Leuk:** leukocytes; **Plts**: platelets; **CD4**: cluster of differentiation *4*; **ULN:** upper limit of normal; **AST**: aspartate aminotransferase; **ALT**: alanine aminotransferase; **INR:** international normalized ratio; **LDH**: lactate dehydrogenase; **Cr:** creatinine; **Albu**: albumin. *Maculopapular or papular rash. **Enlarged lymph nodes. The laboratory threshold for AST was based on a study by de Francesco Daher et al[15].The LDH threshold was arbitrarily selected.

TABLE 3: Multivariable analysis of risk factors associated with disseminated histoplasmosis in AIDS patients in Brazil, 2006-2007.

	Adjusted prevalence ratio (95% CI)
Hepatomegaly	1.96 (1.21–3.16)
CD4 ≤75 cells/µL	2.02 (1.06–3.83)
LDH ≥5x ULN	2.23 (1.44–3.48)
Maculopapular or papular rash	1.70 (1.02–2.83)

AIDS: acquired immunodeficiency, syndrome; **95% CI:** 95% confidence interval; **CD4**: *cluster of differentiation 4*; **LDH:** lactate dehydrogenase; **ULN:** upper limit of normal.

DISCUSSION

Our study found that hepatomegaly, a CD4 count ≤75 cells/µL, LDH level ≥5x the UNL, and a maculopapular or papular rash were significantly associated with DH. These variables may thus be valuable biological markers for decision-making in AIDS patients in endemic areas with few resources.

In 1 year, 48 cases of DH were diagnosed at *Hospital São José*. This high number of cases is likely related to the active identification and investigation of suspected patients in the hospital wards. This finding highlights Ceará as a *Histoplasma* hyperendemic region and suggests that studies should be conducted to better understand the epidemiology of *Histoplasma* infection in the area. We believe that an even higher number of cases might be reported if the most sensitive test – the *Histoplasma* antigen test – was used; however, this test is not available in Brazil.

We found that DH patients were three times more likely to have a temperature ≥38.5°C, compared to the non-DH group. Although fever is a common sign of many opportunistic

infections affecting AIDS patients and was not significant in the multivariable analysis, the intensity of fever could trigger an early suspicion and search for a DH diagnosis in endemic areas. A study conducted by Adenis et al. in 2014 found that patients with histoplasmosis had a significantly higher temperature when compared to patients with tuberculosis (39.5°C *vs* 39.0°C; $p = 0.02$), which corroborates our finding[13].

The main symptoms and signs reported for DH patients in our study were similar to those reported in a study of 200 cases in French Guiana. Almost 90% of the patients in the earlier study had a fever, and half complained of abdominal pain, diarrhea, and cough[14]. In contrast, to the French Guiana study, however, the current work and previous Brazilian studies identified very few patients with enlarged lymph nodes[5,8]. All patients included in the current study were evaluated via physical examinations during the data collection period, and palpable peripheral lymph nodes of any size would have been noted by the investigators. We attribute this difference in the lymph node findings to regional differences in specific fungal strains, rather than an unnoticed physical sign. A large number of our patients were diagnosed with an HIV infection due to the DH episode, consistent with previous studies conducted in South America[14,15].

Skin and mucosal lesions should always be investigated if DH is suspected, as smears and biopsies from these lesions are easily performed and can facilitate a diagnosis. Similar results were observed in a recent study conducted in the South Region of Brazil, which identified skin lesions as a clinical predictor of DH in AIDS patients [odds ratio, 7.0; 95% confidence interval (95% CI): 1.9-27.2], together with oral ulcers and mediastinal lymphadenopathy[16]. The presence of skin lesions varies considerably by region. In Brazilian studies, the occurrence of these lesions varied from 17.3% to 44%[8,17,18]. In contrast, studies from French Guiana described skin lesions as uncommon presentations[2,13,14]. As with the presence of enlarged lymph nodes, these differences in skin involvement have been attributed to genetic variations among *H. capsulatum* strains[19]; however, some argue that skin lesions may indicate an advanced stage of DH with higher fungal dissemination[2].

Previously, an elevated LDH level has been proposed as a diagnostic indicator of DH[10,20]. Patients with histoplasmosis or pneumocystis pneumonia (PCP) were found to have significantly higher LDH levels, and extremely elevated values were more than nine times more likely to be associated with histoplasmosis[20,21]. The sensitivity and specificity of a high LDH level for the diagnosis of severe histoplasmosis were 70% and 80%, respectively[20]. In our study, the association of high LDH levels with DH confirmed these previous findings.

In DH, the liver involvement has been well characterized by the presence of visceral enlargement and laboratory abnormalities [e.g., elevated aspartate aminotransferase (AST), and international normalized ratio (INR)], as demonstrated in the current study and previously by Pontes et al[4].

Patients with DH had lower CD4 counts, indicating advanced immunosuppression. In *Histoplasma*-endemic areas, a CD4 count <150 cells/μL places an AIDS patient at a high risk of DH and is considered an indication for prophylactic treatment[22]. However, as discussed by Nacher et al, histoplasmosis remains underexplored in the Amazon Basin, which increases the challenges associated with diagnosis, treatment and, consequently, prophylaxis[23]. Although the CD4 count is a predictor of the incidence of *Histoplasma* and associated death[22]. this parameter is frequently unavailable at admission in many settings, as many HIV-infected patients with suspected DH either do not know or do not report their HIV status and do not undergo this examination at hospital admission.

In our study, DH patients had a case fatality rate of 20.8%. Higher figures (32.8% and 42.3%) were reported at the same hospital[4,5] and in another study comparing the outcomes in Brazil (39%) and the USA (10%)[19]. A study from French Guiana reviewed 19 years of case histories and reported that in 74% patients with fatal outcomes, histoplasmosis was the first AIDS-defining illness[24]. The higher case fatality rates in Brazil may indicate reduced access to medical care with consequent delays in diagnosis, which contribute to the increased frequency of more advanced disease at hospital admission.

Pleuritic chest pain was more common in patients without DH. In a comparative study of AIDS patients in French Guiana, patients with tuberculosis more frequently presented with cough and/or chest pain, compared to those with histoplasmosis[13]. That same study also found that hepatomegaly, splenomegaly, and anemia were more common in patients with histoplasmosis.

In summary, the presence of hepatomegaly, a maculopapular rash or multiple papular lesions, a low CD4 count, and an elevated LDH level were significant predictors of DH in AIDS patients admitted to a reference hospital. In the absence of advanced diagnostic methods, the identification of these clinical and laboratory parameters in a DH-suspected patient will facilitate decision-making, prompt treatment and, consequently, improve prognosis.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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