

Disseminated histoplasmosis in AIDS patients: an urban disease. Experience in a metropolis in the middle east of Brazil

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SUMMARY

Histoplasmosis is a fungal disease commonly observed as an opportunistic disease in AIDS patients. It is a neglected disease in many countries, particularly Latin America, including Brazil. It is related with environmental factors, even in urban areas, where the incidence has increased. Implementing a descriptive ecological study, we performed a retrospective chart review for data collected between January 2003 and July 2014 for AIDS patients with histoplasmosis who lived in Goiânia. The selected cases were georeferenced to analyse the incidence of histoplasmosis in AIDS patients in the metropolitan area of Goiânia. In all, 166 patients (130 men) met the criteria for AIDS and histoplasmosis coinfection. Almost half of the patients (41%) had simultaneous histoplasmosis and AIDS diagnoses. The general mortality was 53% (88 patients). The main symptoms involved the respiratory, gastrointestinal, and cutaneous systems. The distribution of cases included almost all regions of the

urban areas, with some predominance in the eastern and western regions close to areas of environmental degradation, contaminated water sources and unplanned urbanisation. In conclusion, coinfection with HIV and disseminated histoplasmosis is common and associated with high mortality rates in our referral hospital for infectious diseases. Despite being considered as having a predominantly rural epidemiology, many patients reported living in urban areas such as Goiânia and Aparecida de Goiânia. Our findings suggest the need for environmental studies to evaluate environmental contamination and possible local risk factors for *H. capsulatum* infection in addition to serological surveys to determine the prevalence of this infection in the studied cities.

Keywords: acquired immunodeficiency syndrome, histoplasmosis, georeferencing, urban population, environment.

INTRODUCTION

Histoplasmosis is a fungal disease caused by *Histoplasma capsulatum* [1]. It is an endemic disease in many countries, including in the

Mississippi and Ohio river valleys in the United States and in Central and South America [2]. The environmental growth of *H. capsulatum* is closely related with ambient factors, and it is found in regions with acidic soil, hot and humid air temperatures, high rainfall, and the presence of bat guano and bird droppings [1]. The infection is usually related with employment and recreational activities in rural areas, such as those with poultry or caves [3, 4].

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Although it can cause disease in both immunocompetent and immunocompromised people, it can result in severe diseases in immunocompromised people, in whom there is high mortality and morbidity with the disseminated form [5, 6]. With the advent of AIDS, the disease became clinically and epidemiologically important and is considered one of the most important fungal diseases in AIDS patients [7, 8].

In many Brazilian states, there are high rates of histoplasmosis in AIDS patients, particularly at the reference hospital for infectious diseases in which there are many patients from the national public health system; this hospital is situated in Goiânia, the second largest metropolitan city in the middle east of Brazil [5,9]. Several cases are patients with AIDS who report living in urban areas without any apparent risk factors for histoplasmosis. However, the actual epidemiology of the disease is unknown and underestimated.

In this article, we report the clinical and epidemiological analyses of disseminated histoplasmosis (DH) in AIDS patients diagnosed during a 10-year period in the hospital of infectious diseases as well as the evaluation of the urban incidence of the disease through geocoding and spatial analysis.

■ PATIENTS AND METHODS

In this descriptive ecological study, we evaluated cases of histoplasmosis in AIDS patients who were treated at the referral hospital for infectious diseases (Hospital de Doenças Tropicais Dr. Anuar Auad) in Goiânia, Goiás state between January 2003 and July 2014. Goiânia and Aparecida de Goiânia are the largest cities in the metropolitan area of Goiânia. The research protocol was approved by the local ethics committee and by the National Research Ethics Commission (CONEP), and is registered with the General Certificate for Ethics Assessment (CAAE) number: 29587914.1.0000.0034. We included patients of all ages and both sexes living in Goiânia and Aparecida de Goiânia at the time of hospital admission, who had a positive enzyme-linked immunosorbent assay result for human immunodeficiency virus (HIV) infection or another test to confirm the HIV diagnosis according to the diagnostic protocol from the Ministry of Health of Brazil. And confirmed

histoplasmosis according to culture, histopathological tests (bone marrow, skin, and other tissues) tests, detection of fungus in a blood smear, or specific serological tests for histoplasmosis. The study excluded patients without a confirmed diagnosis of both histoplasmosis and HIV infection, as indicated in the previous paragraph.

Questionnaire data were entered into a database and statistically analyzed using SPSS version 20.0 for Windows (IBM Corp, Armonk, NY). Categorical variables are described using frequencies and simple percentages, while continuous variables are reported as means, medians, and interquartile ranges.

The addresses of the medical records were georeferenced and transformed into points based on X (longitude) and Y (latitude) coordinates using ArcGIS version 9.0 for Windows. The maps of Goiânia and Aparecida de Goiânia were obtained from the System of Geoinformation State of Goiás (SIEG), which are available for download and public consultation online: <http://www.sieg.go.gov.br/>. The geocoded databases were attached to the geographic databases of the cities studied, which were obtained from the 2010 Brazilian Institute of Geography and Statistics (IBGE) Census. On the map (Figure 1) each case represented a point, and the Kernel method was used to determine the density of the cases, where red indicates the hot areas, which have the highest density; yellow indicates areas of medium density; and green indicates areas of low density [10].

■ RESULTS

Of the 2285 AIDS cases reported at our referral hospital, of patients who lived in Goiânia and Aparecida de Goiânia, there were 166 cases of DH during the same period (Table 1). All the study patients with DH were classified based on the involvement of more than one organ or system, which was diagnosed by identifying the fungus in an extrapulmonary site. DH up to one year after the diagnosis of HIV or AIDS or DH coinfection was present in 104 patients, and the general mortality was 53% (88 patients). Ceasing antiretroviral therapy was related with DH diagnosis for 64 patients (38.5%). Almost half of the patients (41.5%) were born in Goiânia or Aparecida de Goiânia.

Table 1 - Main clinical and epidemiological characteristics of the study patients.

	Study Period				Total cases	
	2003-2005	2006-2008	2009-2011	2012-2014	n=166	n %
	n=15	n=41	n=54	n=56		
Demographics and HIV characteristics on admission						
Male sex (%)	14	31	44	41	130	78.3
Mean age	40	37.3	33.5	36.8	36.1	
Histoplasmosis on AIDS diagnoses (%)	5	21	17	25	68	41
Abandonment of ARV ¹	9	14	21	20	64	38.5
Average value of LT-CD4 ⁺ (cells. /mm ³)	117.3	44.9	75.4	63.5	70.4	
User drug	5	8	13	6	32	19
Clinical characters of histoplasmosis on admission						
Sepsis	3	9	16	13	41	25
Respiratory symptoms	12	26	34	27	99	59.6
Intestinal symptoms	5	12	18	18	53	32
Hepatosplenomegaly	3	19	16	17	55	33
Acute kidney injury	0	5	8	8	21	12.6
Skin lesions	7	13	16	13	49	29,5
Neurologic symptoms	3	7	11	7	28	17
Histoplasmosis confirmatory tests						
Culture	10	30	51	50	141	85
Fungal research on smear blood	4	9	13	11	37	26,2
Histopathological	5	13	5	7	30	18

Legend: ¹ARV: antiretroviral therapy; ² LT CD4+: lymphocytes T CD4+.

The disease was predominant in male sex (sex ratio of 3.6 to 1), and the mean age was 36.1 years (\pm 8.9 years). In 41% of the cases, the patients were diagnosed with AIDS and histoplasmosis simultaneously. The average measure of LT CD4⁺ was 70.1/mm³. Respiratory symptoms were the most common clinical presentation (59.6%) followed by hepatosplenomegaly (33%) and skin lesions (29.5%). Sepsis was diagnosed on 25% of the patients. Culture was the most frequent confirmatory test (Table 1). Most part of patients was treated with amphotericin B deoxycholate, with low response rates because of the severity of disease and the drug toxicity.

The georeferencing of cases highlighted that some cases of histoplasmosis in AIDS patients were distributed in almost all regions of the urban area, with some predominance in the eastern and western regions (Figure 1). In these regions are located the main rivers that cross the cities, and are char-

acterized by important environmental degradation and high population concentration.

■ DISCUSSION

In the present study, 53% of the patients with concurrent DH and AIDS died. These were primarily young men (78.3%), although two cases were children. This finding supports the previously reported DH-related mortality rates of 50-70% in HIV patients, in whom DH can cause severe disease [5,11,12]. The average CD4 value at DH diagnosis was 70 cells/mm³, like those reported in most studies, in which a CD4 level <100 cells/mm³ or <200 cells/mm³ is reportedly a risk factor for death or disseminated disease, respectively [8,13,14].

The main symptoms involve the respiratory (60%), intestinal (31.9%), and cutaneous (29.5%)

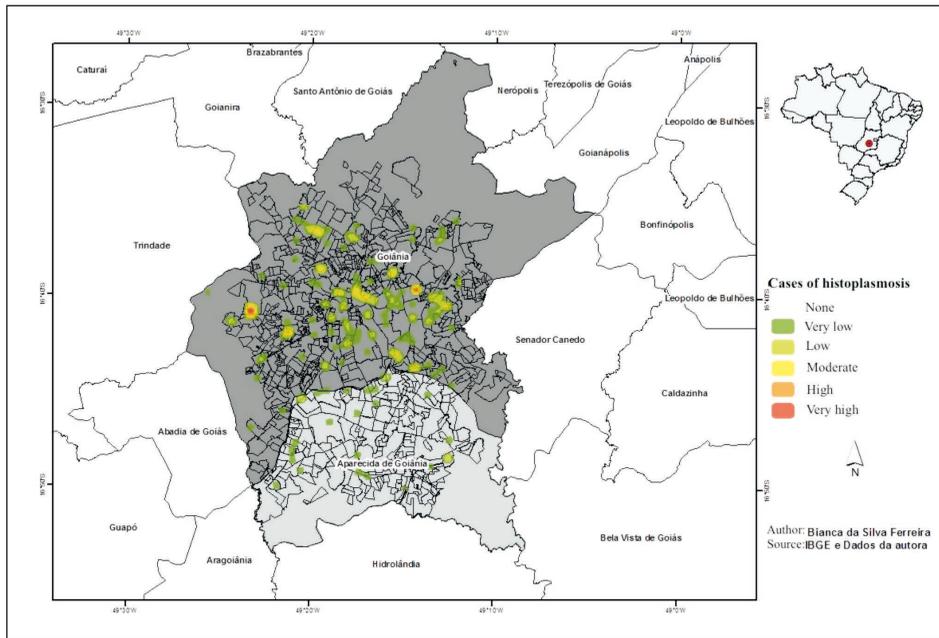


Figure 1 - Map of histoplasmosis outbreaks in Goiânia and Aparecida de Goiânia.

systems. However, potentially owing to phylogenetic differences, these systems are involved in fewer cases in the United States, where respiratory symptoms account for 42-47%, intestinal symptoms for 2-8%, and cutaneous symptoms for 1-4% of cases [13].

Underdiagnosis often occurs because of the relative difficulty of diagnosis. Radiological and laboratory tests (blood count, transaminase levels, lactate dehydrogenase levels, liver function) are nonspecific, and the clinical symptoms are severe; therefore, it is often confused with tuberculosis or pneumocystis [14-16].

The mapping of diseases such as histoplasmosis enables the understanding of the relationship between man and the environmental factors that influence the disease epidemiology, identification of social and environmental risk factors, and future evaluation of the relationship between the disease and the urban environment [17].

The phenomenon of urbanization, especially when it is poorly planned such as in many Brazilian cities, causes several important changes in the environment. The natural habitat of many animal species is lost, including those for birds and bats that have to then readjust to the urban environment to survive [18]. This contributes to the emergence and spread of various diseases in urban areas; an example is histoplasmosis, which occurs

particularly among HIV patients, with high morbidity and mortality, resulting in a public health problem.

It is likely that a number of patients acquired the mycosis in urban areas of the cities where the study occurred; they have favorable environmental conditions for contamination, such as unplanned urbanization with high population density, contaminated water in the main rivers, and irregular occupation of environmental workers in preservation areas. Because some of the cases were children, it is probable that the fungal contamination in the urban environment occurred recently.

As it was not possible to assess the epidemiological history of the patients owing to the retrospective design, we cannot say that all patients acquired histoplasmosis in the urban areas of Goiânia and Aparecida de Goiânia. There are insufficient data at present to establish the actual epidemiology of the disease in the studied urban areas. However, the fact that nearly half of patients were born in the studied cities suggests that the infection in these patients occurred in the studied regions.

To conclude, HIV/DH coinfection is common and associated with high mortality rates in our referral hospital for infectious diseases. Despite the expectation that histoplasmosis is a predominantly rural epidemiology, a number of patients

reported living in urban areas such as Goiânia and Aparecida de Goiânia. However, because the areas with the greatest number of cases have been environmentally degraded, with unplanned urbanization and pollution of water sources, these epidemiological findings suggest the need for environmental studies to determine the level of environmental contamination and possible local risk factors for infection with *H. capsulatum*; in addition, serological surveys are needed to determine the prevalence of this infection in the studied cities, which could contribute to the precise characterization of this coinfection.

Authors' contributions

J.A.A.F. and B.S.F. conceived and designed the study. N.M.P., L.M.G., B.B.L. for data collection. E.D.N. and L.E.R. performed the spatial analyses and preparation of study map. B.S.F. performed the statistical analysis under and wrote the first draft of this manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

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