



## Case report

## Disseminated histoplasmosis in Peruvian non-HIV patients: an underrecognized endemic disease

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## ABSTRACT

**Background:** Histoplasmosis is a worldwide mycosis with endemic areas throughout Latin America. Disseminated histoplasmosis (DH) has been described in Peru, but there are few reports about its clinical presentation in non-HIV patients.

**Methods:** Case series was done with review of clinical and laboratory charts from Hospital Cayetano Heredia and Instituto de Medicina Tropical Alexander von Humboldt. Eight patients meet the case definition: HIV negative test and definitive diagnosis of DH (isolation of *H. capsulatum* in culture and/or presence of yeasts on the histopathology), between 2000-2019.

**Results:** Six were men with median age of 53 years [IQR 35-63,5], most of them were farmers or merchants and with a history of being born in or traveled to the jungle. The median time of illness until diagnosis was 390 days [IQR 60-730] and in 7 out 8 cases the diagnosis was made by isolation of fungi in culture. Isolates required 11 days [IQR 10-18] to become detectable in culture. Six cases had another concomitant disease that probably caused an immunosuppression.

**Conclusion:** DH form occurs rarely in apparently healthy people. In this series, men in their fifties, working in farming or merchant, with history of being born in or traveled to the jungle were the most frequent epidemiological characteristics. Culture and histopathology were used for the diagnosis but obtaining the results required several days. It is necessary the use of other faster techniques and to strengthen the clinical awareness about this disease.

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## 1. Introduction

Histoplasmosis is a worldwide mycosis with endemic areas throughout some regions of the United States and Latin America. It is caused by *Histoplasma capsulatum*, which is found in soils contaminated with excreta of bat and birds [1]. The infection has a wide clinical spectrum from asymptomatic to disseminated forms, that depends on the host's immune response, the size of the inhaled inoculum and the virulence of the fungus. Disseminated histoplasmosis (DH) is rarely diagnosed in apparently healthy or mildly immunosuppressed people [2]. In Peru, there are reports of DH in people living with HIV [3], however no information of this clinical form has been published in non-HIV Peruvian patients.

Culture is the gold standard for the diagnosis of DH because it allows the isolation and characterization of the fungus, but it takes a long time to grow requiring between 4 to 6 weeks. The

histopathology allows detecting the small yeasts in granulomas, which remains as an important diagnostic modality despite its low sensitivity [4,5,6].

We describe the clinical and epidemiological characteristics of DH in non-HIV patients from a single public hospital in Lima, Peru with the aim of improving the knowledge of health workers about this disease.

## 2. Material and methods

This is a cases series study extending from 2000 to 2019, based on the data collected from the clinical and laboratory charts from Hospital Cayetano Heredia and Instituto de Medicina Tropical Alexander von Humboldt and compiling all non-HIV patients with a definitive diagnosis of DH, evaluated in a public hospital in Lima, Peru. This protocol was approved by the Human Research Ethics Committee of the Universidad Peruana Cayetano Heredia.

Definitive diagnosis of DH was defined as isolation of the fungus in culture and/or the visualization of the small yeasts suggestive of *H. capsulatum* using hematoxylin-eosin and periodic acid Schiff's stains in histopathology.

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**Table 1.** Epidemiological and clinical characteristics of eight non-HIV patients with disseminated histoplasmosis.

Case	1	2	3	4	5	6	7	8
<b>Sex</b>	M	M	F	F	M	M	M	M
<b>Age</b>	60	54	67	52	24	36	81	34
<b>Place of acquisition of the disease</b>	San Martin	San Martin/Cuzco	Ayacucho	Huanuco	Ucayali	La Libertad	Junin	Junin
<b>Occupation</b>	Farmer	Merchant	Farmer	Farmer	Farmer	Farmer	Farmer	Farmer
<b>Time of disease (days)</b>	60	730	60	1095	30	730	240	540
<b>Comorbidity</b>	CD4 deficiency	Hypothyroidism Hepatic cirrhosis	Diabetes mellitus	Hypothyroidism Systemic lupus erythematosus	Hemolytic anemia	None	None	HTLV-1 infection, Paracoccidioidomycosis
<b>Mucocutaneous lesion</b>	Absent	Absent	Absent	Absent	Papules	Absent	Anal Ulcer Oral Ulcer	Oral ulcer Skin ulcer Absent
<b>Lymph node</b>	Cervical Inguinal	Absent	Absent	Cervical	Absent	Epitrochlear Inguinal	Absent	Absent
<b>Fever</b>	Yes	Yes	No	No	Yes	No	Yes	No
<b>Initial treatment</b>	Amphotericin B	Amphotericin B	Amphotericin B	Amphotericin B	Amphotericin B	Amphotericin B	Itraconazole	Amphotericin B
<b>30-day outcome</b>	Dead (day 10th)	Alive	Dead (day 15th)	Alive	Alive	Alive	Alive	Alive

### 3. Results

In 19 years, eight cases of DH were identified with a male to female ratio 6:2, with a median age of 53 [IQR 35-65.5] years. Most of the patients were born or traveled to the jungle and probably acquired the fungus in this region [CI 95% 47.4-99.7]. Six patients [75%; CI 95% 34.9-96.8] reported one or two comorbidities All patients were merchants or farmers. The median time of illness until the time of diagnosis was 390 [IQR 90-730] days. Mortality at 30-day was 25% [CI 95% 3.2-65.1] (Table 1). In 87.5% [CI 95% 47.4-99.7] of patients the diagnosis was made by isolating the fungus in culture and just in one patient [12.5%; CI 95% 0.3-52.7], it was confirmed exclusively by histopathology. The mean time of the detection of the fungus in culture was 10.5 [IQR 8.5-12] days (Table 2).

### 4. Discussion

DH usually occurs after spreading and reactivation of a previously acquired infection, in the setting of a decline of cellular immunity. The most common example is DH in patients with HIV/AIDS with low CD4+ T-cell counts and an impairment of Th1/Th17 subtypes function, which is required for an effective response against *H. capsulatum* [7]. The small number of histoplasmosis cases in different reports including non-HIV infected patients may be due to the fact that the spread of the disease has been limited by intact immunity or its mild deficiency preventing its reactivation and/or dissemination. Other reasons for the small number of diagnosed cases could be lack of awareness and misdiagnosis by healthcare workers in rural areas of the Peruvian jungle and lack of sensitive and rapid diagnostic tests.

Most of the patients in this study were male with an average age of 53 years, which is similar to report by Faiolla *et al*, in Brazil and correlates to the occupational risk factor like being a farmer or living in a rural environment [5,16].

Seven of the eight patients probably acquired the disease in cities where they were born or visited (Loreto, San Martin, Huanuco, and Ucayali), located in the jungle at altitudes that vary from 70 to 500 m. a.s.l [2], characterized by having a hot, humid and rainy climate throughout the year, where agriculture is the main source of economic income. Since the 1950s it was already known that some cities in the Peruvian jungle are endemic areas of this disease. Certain studies performed with histoplasmin skin test in those regions found positivity rates up to 42%, and others reported the isolation of *H. capsulatum* from soil samples in the similar areas [8].

The progression of the disease in this series of cases is probably due to the long evolution time as a consequence of a delay in its diagnosis. However, six patients had a previous disease that could have caused a decrease in immunity and therefore allow the spread of the disease. People with diabetes mellitus and uncontrolled hyperglycemia have a higher frequency of severe infections due to abnormal cellular immunity and decreased vascularity but until now, the relationship between diabetes and DH is not fully explained [9].

Other diseases such as systemic lupus erythematosus could be a risk for acquiring infections including DH for an alteration in humoral and cellular immunity like one case presented here [10].

There are coinfections of viruses with other endemic mycosis, as the case 8 of the present report who had an HTLV-1 infection and was concomitantly diagnosed with both endemic fungal infections, histoplasmosis and paracoccidioidomycosis [11]. It is known that HTLV-1 infection, with a prevalence in Peru between 1.3%-3.8%, predisposes to develop adult T-cell leukemia/lymphoma, tropical spastic paraparesis and infections by: *Sarcoptes scabiei*, *Strongyloides stercoralis* and *Mycobacterium tuberculosis*. However, the mechanism by which HTLV-1 carriers may develop fungal infections has not yet been studied [11,12].

There are no specific signs of DH, but fever, lymphadenopathy, and mucosal lesions have been reported in similar proportions in both populations with and without HIV infection, however skin lesions have

**Table 2.**  
Positivity of diagnostic tests in eight non-HIV patients with disseminated histoplasmosis.

Case	Culture	Sample	Growth time (days)	Presence of yeast in histopathology
1	Positive	Bone marrow	18	Lymph node: positive
2	Positive	Bone marrow	11	Not evaluated
3	Positive	Colon biopsy	7	Colon biopsy: positive
4	Positive	Lymph node	11	Lymph node: negative
5	Positive	Blood	13	Not evaluated
6	Not evaluated			Gum biopsy: positive
7	Positive	Anal mucosa	10	Not evaluated
8	Positive	Colon biopsy	10	Colon biopsy: positive

been detected more frequently in patients with HIV infection [14,16]. Subclinical or chronic infection with *Histoplasma capsulatum* is common in persons living in endemic areas whereas clinical presentation in HIV infected individuals were shown to develop rapidly progressive histoplasmosis, this can explain a long time until symptoms appearing in these cases [16], also DH can mimicked malignancy or other infectious diseases like tuberculosis and for that reason is important that health-care workers are aware of the diagnosis of histoplasmosis, especially in endemic areas and the lack of fast and sensitive diagnostic tests can cause delay of the diagnosis and treatment [6,13].

In this report, the median time to obtain the fungus in culture was 10 days. One sample required only 7 days to be detected probably due to the presence of a large fungus inoculum [2]. However, it is known that some isolates can take up to 6 weeks to grow, delaying the diagnosis and therefore the treatment [2,4]. In Peru, the diagnosis of DH in non-HIV patients is still performed using culture or histopathology because the laboratory capacity for a faster and more sensitive diagnostic test, is limited. Despite the IMMY urine *H. capsulatum* antigen enzyme immunoassay (IMMY EIA) has been implemented at the clinical mycology laboratory of the Instituto de Medicina Tropical Alexander von Humboldt for the diagnosis of DH in HIV patients, this test is not available in public hospitals and it needs to be evaluated in non-HIV patients [15].

Liposomal amphotericin B is the recommended drug for the induction treatment of moderate to severe DH [4], otherwise this antifungal drug is not included on the Peruvian essential medicine list medicines and it only can be purchased at high cost in private medical centers. For that reason, seven out of eight patients were treated with amphotericin B deoxycholate, which is available through the public health system, despite of its association with more frequent and severe adverse events [13] compared to other formulations.

## 5. Conclusion

DH in Peruvian non-HIV infected people is rarely diagnosed. It affects mostly people who is usually working in jungle regions and gets exposed to the fungi. The delayed diagnosis is due probably to unawareness of this disease among healthcare professionals and to lack of fast and sensitive testing tools. It is necessary to strengthen the clinical awareness about this disease and implement better diagnostic tests than the conventional ones in the health facilities located in endemic areas. In addition, access to recommended treatment must be guaranteed by the Ministry of Health.

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