



Disseminated histoplasmosis with hemophagocytic syndrome in a patient with AIDS: description of one case and review of the Spanish literature

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Summary

We report a case of disseminated histoplasmosis in a 33-year old Ecuadorian patient with AIDS and a CD4 lymphocyte count of 39 cells/ μ l. He presented with prolonged fever and cough, was diagnosed with hemophagocytic syndrome and multiple organ failure and died 18 days after admission. *Histoplasma capsulatum* was isolated post-mortem from bone marrow biopsy and blood culture.

In a literature review we found 22 published cases of disseminated histoplasmosis in patients with AIDS in Spain since 1988. All but two were men under 50 years old. Nineteen had been born or had lived in endemic areas. The diagnosis of histoplasmosis was established by culture of bone marrow biopsy in 10 cases. Itraconazole was introduced as a second drug after amphotericin B in ten of the thirteen patients who survived.

Key words

Histoplasma capsulatum, Disseminated histoplasmosis, HIV, Hemophagocytic syndrome

Histoplasmosis diseminada con síndrome hemofagocítico en un paciente con sida: descripción de un caso y revisión de la literatura española

Resumen

Presentamos un caso de histoplasmosis diseminada en un paciente ecuatoriano de 33 años, con sida y recuento de linfocitos CD4 de 39 células/ μ l. Al llegar a nuestro hospital refería fiebre prolongada y tos, fue diagnosticado de síndrome hemofagocítico con fallo multiorgánico y falleció a los 18 días del ingreso. El diagnóstico se completó post-mortem, con el aislamiento de *Histoplasma capsulatum* en las muestras de sangre y biopsia medular.

En la revisión de los casos de histoplasmosis diseminada en infectados por el VIH publicados en España desde 1988, encontramos 22 pacientes. Todos excepto dos eran varones menores de 50 años. Diecinueve habían nacido o vivido en áreas endémicas. El diagnóstico de histoplasmosis se realizó por cultivo de biopsia de médula ósea en 10 casos. Diez de los trece pacientes que sobrevivieron habían sido tratados con anfotericina B y, posteriormente, con itraconazol como segundo fármaco.

Palabras clave

Histoplasma capsulatum, Histoplasmosis diseminada, VIH, Síndrome hemofagocítico

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Introduction

Histoplasmosis is a mycosis caused by the dimorphic fungus *Histoplasma capsulatum*. This fungus has been isolated from soil containing bird and bat feces (guano), especially in caves and next to chicken houses. It has been classified into three varieties, two of which are pathogenic to humans: *H. capsulatum* var. *duboisii*, found mainly in Africa, and *H. capsulatum* var. *capsulatum*, distributed worldwide, and endemic to the Mississippi and Ohio River valleys and to Central and South America. Infection results from the inhalation of the fungal microconidia. The development of disease depends on the size of the inoculum and the immune status of the host. Around 1% of infected people develop symptoms that can vary from acute or chronic pulmonary forms, to disseminated histoplasmosis in immunosuppressed hosts [17]. Since 1985, disseminated histoplasmosis is a defining illness of AIDS and, even though highly active antiretroviral therapy (HAART) has reduced the number of infected patients, it remains a significant opportunistic infection in Central and South America. The number of cases, both in endemic and in non-endemic areas, has grown since the first case reports in the US around 1980 [28].

Reactive hemophagocytic syndrome has multiple etiologies (infectious, malignant or autoimmune) and is, in many cases, associated with organ failure [30]. It has also been described in patients with severe forms of histoplasmosis and is often underdiagnosed because clinicians are unfamiliar with it.

We present a new case of disseminated histoplasmosis with reactive hemophagocytosis in an immigrant patient from Ecuador infected by HIV and a review of the Spanish literature.

Case report

A 33-year-old man was admitted to our hospital in February 2006 for evaluation of a 2-week intermittent fever. Born in Ecuador, he had been living in Spain for 5 years but had visited his home country several times. The most recent visit had been four months before this episode. He was heterosexual and was employed as a truck driver.

The patient had been diagnosed of HIV infection in 2002 but was not treated with HAART. In November 2005, he presented at our hospital with fever and haemoptysis and was diagnosed of microbiologically proven disseminated tuberculosis (TB) and AIDS, starting anti-TB therapy and prophylaxis with co-trimoxazol. He had an HIV viral load higher than 100,000 copies/ml and a CD4 lymphocyte count of 39 cells/ μ l.

By the time he arrived to our hospital in February 2006, the patient referred a daily productive cough with intermittent haemoptysis, but no chest pain, dyspnea, diarrhea or weight loss. Findings on a physical examination were unremarkable, except for a temperature of 40 °C. He had been treated 10 days with azithromycin, with no apparent response.

Laboratory tests revealed a leukocyte count of 2000/mm³, 73.3% polymorphonuclear neutrophils, 20.8% lymphocytes and 5.9% monocytes; 107,000 platelets/mm³; a 12.3g/dl hemoglobin level; and elevated acute phase proteins (serum lactate dehydrogenase 1047 IU/l; fibrinogen 413.5 mg/dl; C-reactive protein 92.7 mg/l). Chest radiography was normal, but chest computed tomography showed extensive paratracheal, periaortic and retroperitoneal adenopathy. Bacterial and mycobacterial smears and cultu-

res from blood, respiratory samples and bone marrow biopsy were negative. Serologic tests for HCV, HBV, HSV, CMV, VVZ, EBV, *Toxoplasma*, *Leishmania* spp, *Treponema pallidum*, *Cryptococcus neoformans* and *Brucella melitensis* were also negative.

The bone marrow biopsy specimens demonstrated hemophagocytosis and, in one bone marrow sample, staining with Giemsa showed extracellular rounded forms that could not be identified.

The situation of the patient worsened, despite the administration of levofloxacin and imipenem. Having been diagnosed of hemophagocytic syndrome with multiple organ failure, the patient was admitted to the intensive care unit on day 13, where he died 5 days later.

On day 18 of admission, yeasts grew in the blood samples cultured in Bactec 13A vials for mycobacteria. Budding yeasts were also observed after 20 days of incubation of the bone marrow samples on Sabouraud dextrose agar at 37 °C. When left at room temperature, the yeasts turned into a white cottony mould. Microscopic observation of the septate fungi hyphae and tuberculate macroconidia allowed the identification of *Histoplasma capsulatum*. The diagnosis was then confirmed morphologically (Microbiology Department, Rovira i Virgili University, Reus) and by PCR assay of three serum samples (Microbiology Department, National Microbiology Laboratory, Madridahonda).

A total of 24 diagnoses of disseminated histoplasmosis were registered in the AIDS National Epidemiological Database of Spain between 1998 and 2004 [37]. In a review of the literature using Medline and Google websites, we found 22 reported cases of this disease in patients infected with HIV in our country since 1988 [1-5,9-10,12-13,21,25,29,31-33,35-36]. The characteristics of these cases, together with those of the current patient, are presented in table 1.

Discussion

Infection with *H. capsulatum* results from the inhalation of its microconidia through day-to-day activities in areas where it is endemic or while removing soil from caves and old buildings with guano [17]. The description of some cases in non-endemic regions suggests the existence of environmental spots that allow the growth of the fungus [38]. Other possible methods of transmission that have been proposed are through inhalation of contaminated cocaine from South America [5], parenteral transmission after organ transplantation [20] or by sharing needles with an infected patient [35]. In countries such as Spain, where the fungus is not widespread, the disease affects mainly immigrants or travelers who have lived in endemic areas and have either been exposed to a large inoculum of the fungus or are immunosuppressed. In the series reviewed, all patients but two were men under 50 years old, and only one case corresponded to an infant. Including our patient, 20 (87%) had been born or had lived in endemic areas or tropical countries. The occupational exposure risk of the 3 patients who had not traveled to endemic countries is unspecified. One of them had inhaled cocaine. All 3 of them were injection drug users, and one of them had shared needles with a patient who died of disseminated histoplasmosis. These data support the idea of possible parenteral transmission.

In patients with disseminated histoplasmosis, fever is the most common symptom. They may present with weight loss, anorexia, cough, nausea, vomiting, diarrhea and abdominal pain. On physical examination, patients

Table 1. Epidemiological data, diagnosis and outcome of AIDS patients with histoplasmosis in Spain.

Case	Home country/ Travel History	Age	Sex	CD4	Fungus isolation specimen	Antifungal treatment	Outcome	Reference
1	Argentina	44	M	98	SB, RS	AmB	Death	[13]
2	Argentina	38	M	ND	SB, RS, BC, BMB	AmB and ketoconazole	Survival	[29]
3	Uruguay	51	F	6	SB, BC, BMB, CSF, urine	AmB and itraconazole	Survival	[3]
4	None	24	M	ND	BMB, CSF (postmortem)	No	Death	[2]
5	Lived 2 years in Guatemala	28	M	ND	SB	AmB and itraconazole	Survival	[10]
6	Lived 8 years in Guatemala	31	M	39	RS, adenopathy	AmB and itraconazole	Survival	[32]
7	Argentina	36	M	35	SB, BMB	AmB	Death	[4]
8	Argentina	39	M	38	SB, tracheal biopsy	AmB and itraconazole	Survival	[4]
9	Travels frequently to South America	49	M	32	Necropsy (lung, spleen, liver)	No	Death	[4]
10	Gambia	37	M	50	Necropsy (brain)	No	Death	[4]
11	None	32	M	12	BMB	AmB and itraconazole	Survival	[33]
12	Venezuela	38	M	9	Liver biopsy (postmortem)	No	Death	[31]
13	Travels frequently to South America and Africa	44	M	10	BMB, BC	AmB and itraconazole	Survival	[5]
14	Argentina	49	M	ND	SB	itraconazole	Survival	[5]
15	Caiman Islands (Caribe)	35	M	16	BC, supraclavicular adenopathy	AmB and itraconazole	Survival	[1]
16	None	43	M	30	BMB, RS	AmB and itraconazole	Survival	[35]
17*	Travels frequently to Nicaragua	ND	M	ND	ND	ND	Death	[35]
18	Colombia	25	M	63	IB	Surgery and itraconazole	Survival	[9]
19	Ecuador	11	M	5	Necropsy	No	Death	[12]
20	Ecuador	23	M	17	BMB, BC	AmB	Death	[36]
21	Ecuador	25	M	11	BMB	AmB and itraconazole	Survival	[25]
22	Nicaragua	39	F	34	BMB, cervical adenopathy, BC	AmB and itraconazole	Survival	[21]
23	Ecuador	33	M	39	BMB, BC	No	Death	current

M: male; F: female; SB: skin biopsy; RS: respiratory samples (includes bronchial aspirate, bronchoalveolar lavage and transbronchial biopsy); BC: blood culture; CSF: cerebral spinal fluid; BMB: bone marrow biopsy; IB: intestinal biopsy; ND: no data available; AmB: amphotericin B.

* Brother of case number 16. Shared needles with him. Died of disseminated histoplasmosis.

may have adenopathy, hepatosplenomegaly and, less frequently, oral ulcers and a maculopapular rash affecting face and trunk [27]. Clinically, histoplasmosis can mimic TB [19], as was appreciated in our patient when he presented with fever and intermittent hemoptysis, and should be part of the differential diagnosis, together with different non-endemic mycoses, nocardiosis, rhodococcosis and non-infectious diseases such as lymphoma or other neoplasm, in a patient with symptoms compatible with TB that does not respond to correct anti-TB treatment.

Chest radiography findings may be normal or show a diffuse nodular infiltrate or cavitory lesions [14]. Laboratory evaluation may reveal abnormal liver function test results and pancytopenia due to involvement of the liver and bone marrow. Reactive hemophagocytic syndrome in patients with severe forms of histoplasmosis has also been described, and the presence of fever and cytopenia in patients with AIDS can be a clue to its diagnosis [18]. Hemophagocytosis is defined as the consumption of hemopoietic cells by non-malignant phagocytes and can occur as a result of multiple etiologies (viral, bacterial, parasitic, malignant, autoimmune or familial). Hemophagocytic syndromes are associated with a high mortality dependent on etiology and degree of associated organ failure. In some areas of South America, disseminated histoplasmosis is the most frequent opportunistic infection in severely immunosuppressed HIV infected patients with fever and cytopenia [24]. Hemophagocytosis in these patients is frequent, although not specific of diagnosis, and disseminated histoplasmosis should be included in the causes of pancytopenia in patients with AIDS [22]. To our knowledge, the case we report is the first case of hemophagocytosis in the setting of disseminated histoplasmosis in an AIDS patient published in Spain. Another case, in a patient from Ecuador, was reported in the 22nd Congress of the Spanish Society of Anatomic Pathology but has not been published [7]. Both patients died in a short period of time after admission to the hospital.

In the diagnosis of disseminated histoplasmosis, the "gold standard" is a culture of a body sample, mainly of the skin lesions, bronchoalveolar lavage, bone marrow or blood. *H. capsulatum* grows in living tissue or in culture at 37 °C as a small, round to oval budding yeast, and in soil or cultures at temperatures below 30 °C as a white, cottony mould with a pale brown transverse on Sabouraud agar. The 4-week incubation period required for culture is not practical in severe cases, so other diagnostic techniques have to be used. Furthermore, skin tests are not useful; fungal staining of tissue or blood has lower sensitivity than culture, and serum antibody tests can yield false-positive and false-negative results. The detection of antigen in urine sample is rapid, sensitive and can be useful in monitoring therapy, but should be confirmed with other serologic and culture data [17]. Even though no PCR assay for routine use is commercially available, real-time and semi-nested PCR assays have adequately identified *H. capsulatum* from cultures of bone marrow biopsies, bronchoalveolar lavage and blood [23]. A new real-time PCR-based assay which detects up to 1 fg of *H. capsulatum* DNA per µl of sample, particularly when respiratory secretions or bone marrow samples are analyzed (less reliable in serum), has recently been described [6]. These findings demonstrate that PCR techniques could be useful as rapid diagnostic and confirmation methods. In the series reviewed, the diagnosis was established mainly by culture of bone marrow biopsy (11 cases), skin lesions (7 cases), blood culture (5 cases) and respiratory specimens (4 cases). The diagnosis was achieved on autopsy or after the death of the patient in six cases, with the disease not being suspected while the patients were alive. The diagnosis of HIV infection and histoplasmosis coincided in seven patients.

Treatment is required in patients with disseminated histoplasmosis, especially in those with HIV infection and a CD4 lymphocyte count below 150 cells/µl, in whom the disease is often fatal if untreated [17]. Intravenous amphotericin B (0.5-1mg/kg daily) is the treatment of choice in

severely ill or immunocompromised patients, switching to oral itraconazole (200 mg twice a day) once the condition of the patient has stabilized. Liposomal amphotericin B, was less toxic than conventional amphotericin B in a double-blinded, multicenter clinical trial [16]. Duration of treatment depends on the severity of the disease and the immune status of the patient. Patients with AIDS and disseminated disease typically need 12 months of initial therapy followed by lifelong maintenance using itraconazole therapy to prevent relapse, although some studies suggest that it is possible to interrupt secondary prophylaxis when the patient has responded to HAART, is clinically asymptomatic and has a CD4 lymphocyte count above 150 cells/ μ l [15,26,34]. Other treatment options include fluconazole as a second-line antifungal in patients who are intolerant to both itraconazole and amphotericin B, and posaconazole, which has proven to be effective for patients in whom therapy with amphotericin B, fluconazole or itraconazole has failed [39]. In the series reviewed, the CD4 lymphocyte count was below 150 cells/ μ l in the 18 cases in which this data is available, and below 50 cells/ μ l in fourteen of them. Treatment was established in 13 patients with CD4 lymphocyte count below 150 cells/ μ l. The clinical situation of the patient allowed the introduction of a second drug in eleven of the thirteen patients that survived. The other patient who survived had previously been treated surgically by resection of the small bowel and had then received itraconazole. Of the 5 patients whose CD4 lymphocyte count is unknown, only the three who were treated survived, one of them having received itraconazole therapy alone. This data shows the importance of starting therapy with amphotericin B as soon as possible and then continuing with itraconazole, since all the patients who did not receive any antifungal therapy, or were treated with amphotericin B alone, died. Moreover, all those who received itraconazole survived and did not present relapse in at least 6 months of secondary prophylaxis.

The mortality observed in the series reviewed was 43.5%. This high mortality rate is similar to that reported in other two studies, in which 40% of a total of 25 cases and 32% of 164 HIV-infected patients with disseminated histoplasmosis died [8,11].

In summary, disseminated histoplasmosis should be part of the differential diagnosis in any patient with AIDS and a CD4 lymphocyte count below 150 cells/ μ l, who has prolonged fever, and who has traveled or has lived in an endemic area. However, it should not be disregarded in intravenous drug users or patients with tuberculosis-like symptoms who do not respond to anti-TB therapy, independently of travel history. In HIV positive patients with low CD4 lymphocyte count and fever, any new or unspecific skin lesion, bone marrow biopsy and blood samples should be cultured since this procedure can lead to the diagnosis of the disease. New PCR techniques are encouraging and could be useful as rapid diagnostic and confirmation methods. Since the diagnosis of the disease can be delayed, antifungal therapy should be initiated as soon as possible in these patients. Disseminated histoplasmosis should be included in the causes of pancytopenia in patients with AIDS, where the presence of hemophagocytosis correlates with poor prognosis.

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