# Histoplasmosis Among Human Immunodeficiency Virus-Infected People in Europe

## *Report of 4 Cases and Review of the Literature*

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**Abstract:** We reviewed the clinical, microbiologic, and outcome characteristics of 72 patients with human immunodeficiency virus (HIV)-associated histoplasmosis (4 newly described) reported in Europe over 20 years (1984–2004). Seven cases (9.7%) were acquired in Europe (autochthonous), whereas the majority involved a history of travel or arrival from endemic areas. The diagnosis of progressive disseminated histoplasmosis (PDH) was made during life in 63 patients (87.5%) and was the acquired immunodeficiency syndrome (AIDS)-presenting illness in 44 (61.1%). Disease was widespread in 66 patients (91.7%) and localized in 6 (8.3%), with the skin being the most frequent site of localized infection. Overall skin involvement was reported in 47.2% of the patients regardless of whether histoplasmosis was acquired in Africa or South America. Reticulonodular or diffuse interstial infiltrates occurred in 52.8%. The diagnosis was made during life by histopathology plus culture in 44 patients (69.8%), histopathology alone in 18 (28.5%), and culture alone in 1 (1.5%). During the induction phase amphotericin B and itraconazole (74.6%) were the single most frequently used drugs. Both drugs were also used either in combination (10.2%) or in sequential therapy (11.8%). Cumulative mortality rate during the induction phase of treatment was 15.2%. Overall, 37 patients died (57.8%); death occurred early in the course in 18 (28.1%). Seven of 40 patients (17.5%) who responded to therapy subsequently relapsed. Autopsy data in 13 patients confirmed the widespread disseminated nature of histoplasmosis (85%) among AIDS patients with a median of 4.5 organs involved. The results of the present report highlight the need to consider the diagnosis of PDH among patients with AIDS in Europe presenting with a febrile illness who have traveled to or who originated from an endemic area.

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**Abbreviations:** AIDS = acquired immunodeficiency syndrome; CMV = cytomegalovirus, *Hcc* = *H. capsulatum* var. *capsulatum*; *Hcd* = *H. capsulatum* var. *duboisii*; HIV = human immunodeficiency virus; PCP = *Pneumocystis* pneumonia; PCR = polymerase chain reaction; PDH = progressive disseminated histoplasmosis; PR = present report.

## INTRODUCTION

Histoplasmosis is an infection caused by a dimorphic fungus, *Histoplasma capsulatum*, which is responsible for a progressive disseminated disease among human immunodeficiency virus (HIV)-infected individuals who live in or have traveled in geographic areas where the fungus is endemic[72,83,84]. Two varieties of the fungus are pathogenic in humans: *H. capsulatum* var. *capsulatum (Hcc)* has been reported in at least 60 countries belonging to all of the continents, but is endemic in the United States (especially in the Mississippi and Ohio river valleys), and in Central and South America; *H. capsulatum* var. *duboisii (Hcd)* is endemic in central and west areas of Africa (between the latitude 15 °N and 10 °S) as well as in the island of Madagascar[37].

Progressive disseminated histoplasmosis (PDH) has been included among the illnesses defining acquired immunodeficiency syndrome (AIDS) since 1987[16]. In endemic areas, up to 5% of HIV-infected individuals develop PDH as a consequence of reactivation or acute infection[40,54,83], while in a few cities the incidence may be as high as 25%[84,85]. The disease has been most completely described in reports from the United States, South America, and South Africa[21,40,49,65,83,84]. In Europe, PDH is rare in patients with AIDS, occurring mostly in patients who have traveled to or who originated from countries endemic for the disease[9].

Because immigration from endemic areas to Europe is increasing, physicians in Europe need to become more familiar with the manifestations and the approach to diagnosis of PDH. Herein we review AIDS-associated PDH reported by European authors between 1984 and 2004, and report 4 additional cases.

## PATIENTS AND METHODS

We here describe 4 patients with a diagnosis of AIDS-associated PDH seen at our institution. For the purpose of

this review, histoplasmosis was defined as any cultures positive for *H. capsulatum* or histopathologic findings of organisms whose morphology was consistent with *H. capsulatum*. The histopathologic diagnosis of histoplasmosis due to *Hcc* was based on the identification of tissue yeast forms measuring 2–4 μm in diameter, whereas *Hcd* was identified by larger yeasts (8–15 μm). A case was considered an expression of localized disease when a single site was involved in the absence of any signs and symptoms indicative of systemic involvement (for example, fever, weight loss, hepatomegaly, splenomegaly, pancytopenia). The demonstration of the fungus from blood, bone marrow, or from 1 site plus systemic complaints or 2 noncontiguous sites was considered indicative of disseminated disease.

Anemia was defined as a hemoglobin value of less than 10 g/L, leukopenia as less than 4000 leukocytes/μL, and thrombocytopenia as less than 150,000 platelets/μL. The concurrence of anemia, leukopenia, and thrombocytopenia was defined as pancytopenia.

The previously described cases of histoplasmosis in patients with HIV infection/AIDS diagnosed in Europe from 1984 to 2004 were identified through the MEDLINE (National Library of Medicine, Bethesda, MD) database using the key words ''histoplasmosis,'' ''Europe,'' ''AIDS,'' ''imported mycoses''. Additional cases were identified by reviewing the reference lists of the original articles. Papers published in English, French, Spanish, Italian, and German medical journals were considered. Reports in languages other than English and Italian were translated by physicians fluent in these languages. A manual search of the abstracts published in the book of abstracts of the European Conference on Clinical Aspects and Treatment of HIV Infection was also made to identify additional cases. We found some duplicate cases described in both the national language and in English: in these cases, only the English report was considered.

## CASE REPORTS

### Case 1 (Patient 69, Table 1)

A 29-year-old Brazilian transsexual male living in Italy was hospitalized in April 1993 with a 4-day history of abdominal pain, nausea, diarrhea, and high-grade fever; AIDS had been diagnosed 1 year before, at the time of diagnosis of *Pneumocystis jiroveci* pneumonia (PCP) (formerly *Pneumocystis carinii* pneumonia), after which he was treated with zidovudine (1000 mg/d) and cotrimoxazole for secondary PCP prophylaxis. The patient was emaciated, dehydrated, and had a fever of 40.1 °C; a painful 3-cm mass was found in the left lower quadrant of the abdomen and erythematous papular skin lesions were observed on his trunk, knee, elbow, and buttocks. Hemoglobin was 11.1 g/dL; white blood cells (WBC) 5300 cells/μL; platelet count 305,000 platelets/μL; lactate dehydrogenase (LDH) 661 IU/L; CD4 cells/μL 13 (1.7%) and CD8 cells/μL 562 (73.3%). Chest radiogram was normal but abdominal ultrasound showed hepatosplenomegaly and conglomerated hypodense lymph nodes in the left lower abdomen measuring 3 cm in diameter. Therapy with mezlocillin and metronidazole was started for a presumed intraabdominal infection. Cytomegalovirus (CMV) retinitis was diagnosed and ganciclovir therapy was added. A bone marrow biopsy showed a myelodysplastic picture without granuloma, and histopathology for opportunistic pathogens, including fungi, was negative; the results of a CT scan of the head and a lumbar puncture (performed because of an episode of seizure) were unremarkable. The patient remained febrile and developed respiratory distress associated with bilateral interstitial infiltrates. His clinical condition rapidly deteriorated, and the patient died with a sepsis-like picture 14 days after admission. A postmortem examination revealed a picture of PDH due to *Hcc* with lung, liver, spleen, and intraabdominal lymph nodes involvement.

### Case 2 (Patient 70, Table 1)

A 42-year-old Italian male intravenous drug user was hospitalized in December 1997 because of progressive illness with fever, asthenia, productive cough, dyspnea, and skin lesions. Temperature was 38.7 °C and diffuse papulonodular lesions, up to 2–3 cm in diameter, were present on the face, trunk, and arms. A chest radiogram showed diffuse bilateral interstitial infiltrates. LDH was 2047 IU/L; Hb 9.4 g/dL; platelet count 43,000/μL; and WBC 2690/μL). HIV serology was positive and CD4 count was 9/μL). He traveled extensively and had worked in South America until 1993. Cotrimoxazole, ceftriaxone, and gentamicin were initiated pending the results of blood cultures, bronchoscopy, and skin biopsy. During the following days, he rapidly deteriorated with spiking fever and a sepsis-like picture (acute respiratory distress, acute renal failure, and metabolic acidosis). Skin biopsy showed necrotizing vasculitis without granulomas, and yeast-like organisms 3–4 μm in diameter were seen with periodic acid-Schiff (PAS) and Giemsa. The bronchoalveolar lavage was microscopically negative for *P. jiroveci* and acid-fast bacilli, but Grocott methenamine silver stain showed small yeast-like (2–4 μm) organisms. *Hcc* was subsequently isolated from blood cultures and the skin biopsy. Amphotericin B colloidal dispersion (ABCD 5 mg/kg per day) was started and the patient improved within 3 days. After 24 days of therapy with ABCD (17 d) and itraconazole 400 g/d (7 d), the patient was discharged with the nearly complete resolution of the skin lesions. In December 1999, he was readmitted with fever, skin lesions, and pancytopenia having been nonadherent with antiretroviral therapy and itraconazole for the past year. *Hcc* was again cultured from blood, and skin biopsy showed yeast-like organisms compatible with *Hcc*. The patient was treated with oral itraconazole 600 mg/d and vancomycin plus rifampicin for concomitant *Corynebacterium* spp bacteremia. After discharge he was lost to follow-up.

### Case 3 (Patient 71, Table 1)

A 29-year-old Brazilian woman, who had been living in Italy for 16 months, was hospitalized in February 1998 because of a 2-week history of high-grade fever (40 °C) unresponsive to amoxicillin-clavulanic acid. She also reported abdominal pain, nausea, vomiting, productive cough, and weight loss. She was hypotensive (80/60 mm Hg) and exhibited hepatomegaly, abdominal tenderness, and a 4 × 7 cm skin ulcer in the pubic region. A chest radiogram showed bilateral diffuse reticulonodular infiltrates with mediastinal enlargement. Laboratory abnormalities included Hb 8 g/dL; WBC 20,370/μL; blood urea nitrogen 139 mg/dL; serum creatinine 2.7 mg/dL; LDH 13,136 IU/L; AST 583 IU/L; ALT 123 IU/L; and finding of disseminated intravascular coagulation.

Treatment with ceftriaxone, amikacin, and clarithromycin was started but was replaced by cotrimoxazole and antituberculous therapy 3 days later when HIV seropositivity was reported. CD4 count was 2 cells/μL, CD8 53 cells/μL. She died 8 days after admission of respiratory and multiorgan failure. Autopsy

**TABLE 1.** Clinical Presentation of 72 HIV-Infected Patients With Histoplasmosis Reported in Europe

| Patient (Ref) | Age (yr)/Gender/ Risk Factor | Country of Origin (Acquisition)*/ Country of Diagnosis/Interval (mo) | CD4/μL/AIDS† | Prominent Clinical Findings |
|---|---|---|---|---|
| 1 (1) | 24/M/IVDA | Spain/Spain/NR | NR/NR | Fv, sk, li, sp, lu |
| 2 (2) | 41/M/NR/ | Germany/Germany | NR/No | Fv, lu, bm |
| 3 (3) | 53/M/Homosexual | Argentina/Italy/(6) | 63/Yes | Fv, sk, bm |
| 4 (4) | 51/F/Heterosexual | Uruguay/Spain/NR | 6/No | Fv, sk, li, sp |
| 5 (5) | 35/M/IVDA | Italy/Italy/ | 4/Yes | Fv, sk, li, sp, wl, lu, ly, t, bm, septic shock |
| 6 (6) | 29/F/Heterosexual/ | Italy/Italy/ | 185/No | Fv, li, sp, lu, wl, bm |
| 7 (6) | 35/M/Transexual | Brazil/Italy/NR | 4/No | Fv, sk, li, ly, bm |
| 8 (8) | 65/M/Heterosexual/ | Belgium (Zaire)/Belgium/NR | NR/No | Fv, wl, bm, lu, gi |
| 9 (10) | 36/M/Homosexual/ | Spain (Argentina)/Spain/(5) | 35/Yes | Fv, ly, li, sk, bm |
| 10 (10) | 39/M/Homosexual/ Argentina/Spain | Argentina/Spain/NR | 38/Yes | Fv, bm, sk, lu |
| 11 (10) | 49/M/Heterosexual/ | Spain (South America)/Spain/NR | 32/No | Fv, bm |
| 12 (10) | 37/M/Heterosexual/ | Gambia/Spain/(60) | 50/Yes | Fv, li, lu, CNS, bm |
| 13 (11) | 44/M/IVDA | Spain (Central America and Africa)‡/Spain/NR | 10/Yes | Fv, wl, gi, li, ly, bm |
| 14 (11) | 49/M/Homosexual/ | Argentina/Spain/NR | 61/Yes | Sk |
| 15 (12) | 33/M/Heterosexual Zaire/Germany | Zaire/Germany/NR | <10/No | Fv, lu, wl, gi, li, ly, lu |
| 16 (13) | 32/F/Heterosexual | Ghana/Germany/NR | 0/Yes | Fv, bm, gi, bm |
| 17 (14) | 43/M/IVDA | Italy/Italy/NR | 70/No | Fv, lu, sp, sk, ly, bm |
| 18 (15) | 31/F/Heterosexual/ Switzerland | Cameroon/Switzerland/NR | 2/No | Fv, CNS, lu, bm, DIC, septic shock |
| 19 (18) | 41/M/Heterosexual | Poland (Zaire)/Belgium/NR | 40/No | Fv, wl, lu, sk, bm |
| 20 (18) | 44/M/Heterosexual | Zaire (Zaire, Rwanda, Cameroon)/Belgium/NR | 4/No | Fv, sk, wl, sp, bm, gi |
| 21 (18) | 41/M/Heterosexual | Belgium (Zaire)/Belgium/NR | 0/No | Lu |
| 22 (20) | 28/M/Transexual | Brazil/Italy/(4) | 3/Yes | Fv, sk, wl, gi, li, sp, bm, septic shock |
| 23 (22) | 28/M/NR | Spain (Guatemala)/Spain/NR | NR/No | Fv, sk, li, sp, gi, lu |
| 24 (23) | 30/M/Bisexual | Cambodia/France/(84) | NR/Yes | Fv, lu, sk, ly, bm |
| 25 (24) | 44/M/NR | Argentina/Spain/NR | 98/No | Fv, sk, lu, ly, li |
| 26 (25) | 30/M/Heterosexual | Zaire//Switzerland/(3) | NR/Yes | Fv, septic shock |
| 27 (29) | 38/M/Heterosexual | Liberia/Switzerland/NR | NR/NR | Sk |

| Histopathology | Culture | Treatment Induction, Total Dose or Daily Dose | Outcome |
|---|---|---|---|
| BM: *Hcc* | CSF: *Hcc* | NT | Died 8 d after hospitalization |
| BM: *Hcc* | BM: *Hcc* | AMFB, 1150 mg | Alive 4 wk after diagnosis |
| Skin: *Hcc* | Skin, blood: *Hcc* | Itraconazole 200 mg/d | Died 8 mo later; ADC |
| Skin: *Hcc* | BM, blood, urine, skin, CSF: *Hcc* | AMFB, NR | Alive 8 mo after diagnosis |
| BM, skin: *Hcc*; autopsy (L, Li, S, skin, T): *Hcc* | Blood, skin, urine: *Hcc* | AMFB 225 mg + itraconazole 2400 mg | Died 8 d after diagnosis |
| Postmortem diagnosis. Autopsy (L, Li, K, Ht, S, Ln): *Hcc* | Negative | NT | Died 2 mo after hospitalization |
| Skin, tonsil, Ln: *Hcc* | Blood, skin: *Hcc* | AMFB, 455 mg→itraconazole 400 mg/d | Alive 4 yr after diagnosis |
| BM: *Hcd*; autopsy (L, Li, S, BM, Ln): *Hcd* | BM, blood: *Hcd* | AMFB, NR | Died 6 d after diagnosis |
| BM, skin: *Hcc*; autopsy (L, Li, BM, S, K, T): *Hcc* | Skin: *Hcc* | AMFB, 100 mg | Died 4 d after diagnosis |
| Skin, oral mucosa: *Hcc* | Skin, oral mucosa: *Hcc* | AMFB, 1500 mg | Died 10 mo after diagnosis; disseminated CMV disease |
| Postmortem diagnosis. Autopsy: (L, Li, S): *Hcc* | - | NT | Died 1 mo after hospitalization; aspiration pneumonia; ADC; histoplasmosis |
| Postmortem diagnosis. Autopsy (CNS): *Hcc* | - | NT | Died of MOF; disseminated CMV disease; lymphoma B; CNS histoplasmosis |
| BM: *Hcc* | BM, BAL, blood: *Hcc* | AMFB, 700 mg →itraconazole 400 mg/d | Alive 10 mo after diagnosis |
| Skin: *Hcc* | Skin: *Hcc* | Itraconazole 400 mg/d | Alive 10 mo after diagnosis |
| BM: *Hcc*; autopsy (L, Li, S, Ln): *Hcc* | - | NT | Died 10 d after hospitalization |
| Colon: *Hcc* | Blood: *Hcc* | AMFB, NR | Alive 8 wk after diagnosis |
| Skin: *Hcc* | Blood: *Hcc* | AMFB, 983 mg →itraconazole 200 mg/d | Alive 1 mo after diagnosis |
| BM: *Hcd* | BM, blood: *Hcd* | ABLC 5 mg/kg per d→itraconazole 400 mg/d | Alive 15 mo after diagnosis; itraconazole discontinued (CD4+ >350/μL) |
| Skin: *Hcc*; autopsy (L): *Hcc* | - | Itraconazole 400 mg/d | Died 4 mo after diagnosis; non-Hodgkin lymphoma; histoplasmosis |
| Skin: *Hcc* | - | Fluconazole 100 mg/d | Died 12 mo after diagnosis |
| Transbronchial biopsy: *Hcc* | - | Itraconazole 400 mg/d | Died 24 mo after diagnosis of disseminated Kaposi sarcoma |
| BM: *Hcc*; autopsy (BM, L, K, S): *Hcc* | Blood: *Hcc;* autopsy (BM, L, K, S): *Hcc* | Fluconazole 200 mg/d | Died 8 d after hospitalization of respiratory failure |
| Skin: *Hcc* | Skin: *Hcc* | AMFB, NR | Died 6 mo later of other causes |
| Skin: *Hcc* | Skin: *Hcc* | AMFB, NR | Died 8 d after diagnosis |
| Skin, BAL: *Hcc*; Autopsy (L, Li, Ln, BM, K, B): *Hcc* | Skin, BAL: *Hcc* | AMFB, NR | Died 8 d after diagnosis |
| Blood: *Hcc* | Autopsy: *Hcc* | NT | Died the same day of diagnosis |
| Skin: *Hcd* | Skin: *Hcd* | Itraconazole 200 mg/d | Lost to follow-up |

*continued*

**TABLE 1.** *(continued)*

| Patient (Ref) | Age (yr)/Gender/ Risk Factor | Country of Origin (Acquisition)*/ Country of Diagnosis/Interval (mo) | CD4/μL/AIDS† | Prominent Clinical Findings# |
|---|---|---|---|---|
| 28 (30) | 24/F/Heterosexual | Brazil/Italy/(18) | 2/No | Fv, bm |
| 29 (31) | 40/F/Heterosesual | Nigeria/Italy/(6) | 39/Yes | Sk |
| 30 (31) | 29/M/Heterosexual | Colombia/Italy/(8) | 22/Yes | Fv, sk, wl, li, sp, lu, bm |
| 31 (32) | 32/M/IDVA | Italy (Morocco; India; Nepal)/ Italy/(48) | 24/No | Fv, sk, ly, lu |
| 32 (32) | 43/M/IVDA | Italy/Italy/NR | 39/No | Fv, sk, lu, bm |
| 33 (32) | 50/M/Homosexual | Venezuela/Italy/NR | 40/No | Fv, lu |
| 34 (33) | 36/M/Heterosexual | Ivory Coast/Italy/(24) | 26/No | Fv, wl, li, ly |
| 35 (34) | 43/F/Heterosexual | Guinea-Bissau/Portugal/NR | 68/No | Fv, gj, wl, bm |
| 36 (36) | NR/M/NR | Germany/Germany/NR | 30/No | Sk |
| 37 (42) | 30/M/NR | Nigeria/Switzerland/(36) | 2/No | Fv, sk, bm, ly, sp, b |
| 38 (43) | 35/M/Heterosexual | Brazil/France/(12) | 10/Yes | Gi, wl, ly |
| 39 (45) | 29/M/NR | Switzerland (Mexico)/ Switzerland/NR | NR/No | Fv, gi, wl, ly |
| 40 (46) | 38/M/Heterosexual | Ivory Coast/France/(6) | 2/No | Fv, lu, wl, sk, li, sp, bm, DIC, renal failure |
| 41 (46) | 41/F/Heterosexual | Guinea-Bissau /France/(72) | 68/Yes | Fv, gi, wl, bm |
| 42 (46) | 34/M/Heterosexual | Ivory Coast/France/(132) | 30/No | Fv, lu, sk, ly, li, sp, bm |
| 43 (47) | 41/M/NR | Congo/France/NR | NR/No | Fv, ly, lu, sk, pc |
| 44 (47) | 27/M/NR | Central African Republic/France/NR | 43/Yes | Fv, sk, gi, bm |
| 45 (47) | 36/M/NR | France (French Guyana)/France/(12) | NR/No | Fv, wl, gi, bm |
| 46 (50) | 37/F/Heterosexual | Zaire/France/NR | NR/Yes | Fv, ly |
| 47 (53) | 40/F/Heterosexual | Nigeria/Italy/(24) | 14/No | Sk |
| 48 (55) | 33/F/NR | Laos/Norway (72) | NR/No | Fv, sk, ly |
| 49 (56) | 29/M/IDVA | Italy (Mexico)/Italy/(1) | 48/No | Fv, lu, ly, wl, li, sp, bm, DIC, septic shock |
| 50 (61) | 35/M/Heterosexual | France (Ecuador; Haiti)/France/(3) | 10/No | Fv, wl, gi, li, sp, bm |
| 51 (62) | 38/M/Heterosexual | Zaire/Belgium/(96) | 160/No | Fv, lu, wl, ly, li, sp |
| 52 (64) | 38/M/Homosexual | Argentina/Spain/NR | NR | Fv, sk, lu, li, sp, bm |
| 53 (66) | 33/M/NR | Colombia/Germany/(12) | 8/Yes | Fv, lu, wl, li, sp, bm |
| 54 (67) | 36/M/NR | Germany (USA)/Germany/NR | 49/Yes | Fv, ly, lu, gi, sp |
| 55 (68) | 36/M/Bisexual | Ghana/Italy/(21) | 352/Yes | Fv, sk, wl, lu |
| 56 (69) | 31/M/NR | Spain (Guatemala)/Spain/NR | 39/No | Fv, ly, lu, li |
| 57 (71) | 32/M/IVDA | Spain/Spain/NR | 12/NR | Fv, lu, li, sp, bm |
| 58 (73) | 34/F/Heterosexual | Zimbabwe/Germany/(36) | 5/No | Fv, sk, wl, bm |
| 59 (75) | 53/M/Homosexual | Germany (USA)/Germany/NR | 20/No | Fv, sk, bm |

| Histopathology | Culture | Treatment Induction, Total Dose or Daily Dose | Outcome |
|---|---|---|---|
| ND | Blood: *Hcc* (postmortem) | Fluconazole 400 mg/d | Died 3 d after discharge of heart and respiratory failure |
| Skin: *Hcc* | Skin: *Hcc* | Itraconazole 400 mg/d | Alive 20 mo after diagnosis |
| Skin: *Hcc* | Skin: *Hcc* | Itraconazole 400 mg/d | Alive 6 mo after diagnosis; relapse 3 mo after diagnosis |
| Skin: *Hcc* | Skin, blood: *Hcc* | AMFB, NR | Alive 7 wk after diagnosis |
| Skin: *Hcc* | Skin, blood: *Hcc* | AMFB, NR | Died 12 mo after diagnosis of PCP and *M. kansasii* disease |
| - | Blood: *Hcc* | Itraconazole, NR | Died 24 mo after diagnosis of Kaposi sarcoma |
| Sputum, Ln: *Hcc* | Sputum: *Hcc* | AMFB, 2850 mg | Alive 6 mo after diagnosis |
| Colon: *Hcd* | | Itraconazole 400 mg/d | Alive 12 mo after diagnosis |
| Skin: *Hcc* | Skin: *Hcc* | NR | NR |
| Skin: *Hcd* | Skin: *Hcd* | AMFB 1 mg/kg per d→itraconazole 400 mg/d | Alive 8 mo after diagnosis; relapse 3 mo after diagnosis (therapy discontinued) |
| Colon: *Hcc* | - | Itraconazole 400 mg/d | Alive 6 mo after diagnosis |
| Ln: *Hcc* | - | AMFB, NR | Alive 4 mo after diagnosis |
| BM, blood, skin: *Hcc* | - | Itraconazole 400 mg/d | Died 11 d after diagnosis |
| Colon: *Hcc* | - | AMFB 1mg/kg per d + itraconazole 600 mg/d | Alive 9 mo after diagnosis |
| BM, Ln, skin: *Hcc* | - | AMFB 1 mg/kg per d→itraconazole 400 mg/d | Alive 5 mo after diagnosis |
| Ln: *Hcc* | Ln: *Hcc* | AMFB, NR | Died of cerebral toxoplasmosis 9 mo after diagnosis |
| BM, skin: *Hcc* | Blood: *Hcc* | AMFB, NR | Died of respiratory failure 9 mo after diagnosis |
| BM: *Hcc* | BM: *Hcc* | AMFB, NR | Alive 5 mo after diagnosis |
| BM, BAL: *Hcc* | - | AMFB, NR | NR |
| Skin: *Hcc* | Skin: *Hcc* | Itraconazole, NR | NR |
| Skin, blood, Ln: *Hcc* | Skin, blood: *Hcc* | AMFB, NR | NR |
| ND | Blood: *Hcc* (postmortem) | NT | Died 5 wk after diagnosis |
| BM, colon, Li, Ln: *Hcc* | - | Itraconazole 100 mg (1 d), 800 mg(1 d), 250 mg | Died of disseminated CMV 7 mo after diagnosis |
| Ln: *Hcd* | BM, Ln: *Hcd* | AMFB, 2500 mg | Alive 11 mo after diagnosis |
| BAL, skin: *Hcc* | BM, blood, BAL, skin: *Hcc* | AMFB, NR | Lost to follow-up |
| BM: *Hcc* | BM, blood: *Hcc;* sputum, BAL (PCR): *Hcc* | LAMFB 3 mg/kg per d | Alive 6 mo after diagnosis |
| Ln: *Hcc* | Blood: *Hcc* | AMFB 662 mg + flucytosine 9.6 g | Relapse 2 mo later (no maintenance therapy); died of *P. aeruginosa* sepsis without relapse 27 mo after diagnosis |
| Skin: *Hcc* | Skin (PCR): *Hcc* | NR | NR |
| BAL, Ln: *Hcc* | BAL: *Hcc* | AMFB, NR | Died some mo later |
| BM: *Hcc* | | AMFB, NR | NR |
| Skin: *Hcc*; autopsy (L, S, Ln): *Hcc*; CMV adrenalitis | Skin: *Hcc* | AMFB 1 mg/kg per d + itraconazole 400 mg/d | Died 15 d after diagnosis |
| BM, li, skin, S: *Hcc* | - | AMFB+ itraconazole, NR | Died 8 mo after diagnosis |

*continued*

**TABLE 1.** *(continued)*

| Patient (Ref) | Age (yr)/Gender/ Risk Factor | Country of Origin (Acquisition)*/ Country of Diagnosis/Interval (mo) | CD4/μL/AIDS† | Prominent Clinical Findings |
|---|---|---|---|---|
| 60 (75) | 31/F/Heterosexual | Germany/(Cuba)/Germany/(24) | 10/No | Fv, gi, bm |
| 61 (76) | 33/M/Homosexual/ | Denmark (Venezuela)/Denmark (24) | 0/Yes | Fv, wl, ly, lu, li, sp, bm |
| 62 (80) | 32/F/Heterosexual | French Guyana/France/NR | 7/Yes | Fv, gi, lu |
| 63 (80) | 30/M/Heterosexual | French Guyana/France/(144) | 6/Yes | Fv, gi, lu, wl |
| 64 (80) | 42/M/Heterosexual | Zaire/France (120) | 38/No | Fv, gi, wl, lu, ly |
| 65 (81) | 36/M/IDVA | Italy (USA)/Italy/(120) | 60/No | Fv, gi, bm, ly, li, sp, CNS |
| 66 (82) | 25/F/Heterosexual | Uganda/UK/(48) | ND/No | Wl, jaw, sp, bm |
| 67 (88) | 35/M/Homosexual/ NR/USA/Germany | USA/Germany/(36) | 18/No | Fv, wl, pc, lu, gi, bm |
| 68 (89) | 34/M/Homosexual | Argentina/UK/NR | NR/Yes | Fv, li, sk, b, gi |
| 69 (PR) | 29/M/Transexual | Brazil/Italy/ | 13/Yes | Fv, GI, LY, LU, LI, SP |
| 70 (PR) | 42/M/IVDA | Italy (Brazil)/Italy/(48) | 4/No | Fv, sk, lu, li, sp, bm |
| 71 (PR) | 29/F/Heterosexual | Brazil/Italy/(15) | 2/No | Fv, gi, ly, li, sp, bm |
| 72 (PR) | 30/M/Heterosexual | Ivory Coast/Italy/(17) | 6/No | Fv, ly, sp, li, bm |

Abbreviations: NR = not reported; NT = not treated; Fv = fever; sk = skin lesions; lu = lung (infiltrates); li = liver (liver enlargement or enzyme elevation); sp = spleen (splenomegaly); ly = lymph nodes (lymphadenopathy); gi = gastrointestinal involvement (abdominal pain, diarrhea, nausea, dysphagia, intestinal lesions); wl = weight loss; bm = bone marrow (anemia, leukopenia, thrombocytopenia, pancytopenia); b = bone (bone lesion); *Hcc* = *Histoplasma capsulatum* var. *capsulatum*; *Hcd* = *Histoplasma capsulatum* var. *duboisii*; *Hcu* = *Histoplasma capsulatum* var. unknown; BM = bone marrow; H = histopathology; MI = microscopy; CSF = cerebrospinal fluid; Cx = culture; K = kidney; Ht = heart; S = spleen; Ln = lymph node; IVDA = intravenous drug abuser; T = testis; HIV-2 = HIV type 2; ADC = AIDS-dementia complex; CMV = cytomegalovirus; MOF = multiorgan failure; CNS = central nervous system; DIC = disseminated intravascular coagulation; MAC = *Mycobacterium avium* complex; BAL = bronchoalveolar lavage; B = brain; PCR = polymerase chain reaction; HCV = hepatitis C virus; AMFB = amphotericin B deoxycholate; ABLC = amphotericin B lipid complex; LAMFB = liposomal amphotericin B; ABCD = amphotericin B colloidal dispersion; (+), combination therapy; (→), sequential therapy.

*(If different from country of origin.)

†Previous diagnosis.

‡Country not specified.

histopathology revealed *Hcc* PDH involving the lung (Figure 1), liver, spleen, heart, lymph nodes, kidney, adrenal glands, brain, stomach, uterus, and ovary, as well as PCP.

## Case 4 (Patient 72, Table 1)

A 30-year-old man from the Ivory Coast who had been resident in Italy for 7 years was hospitalized in May 2003 for fever and weight loss of 1 month's duration. HIV-1 infection was diagnosed in April 2000 when he was evaluated for herpes zoster. He had been taking zidovudine, lamivudine, lopinavir/ritonavir since September 2000 but was nonadherent. CD4 count was 6 cells/μL and HIV RNA 311,664 copies/mL upon admission. Hepatosplenomegaly and generalized lymphadenopathy were present, and laboratory abnormalities included Hb 6.8 g/dL; LDH 1377 IU/L; and serum ferritin 2405 ng/mL. A chest radiogram was normal. Bone marrow biopsy showed granuloma containing acid-fast bacilli and thick-walled, yeast-like PAS-positive organisms 8–14 μm in diameter consistent with *Hcd* (Figure 2). Clarithromycin, ethambutol, ciprofloxacin, and oral itraconazole 400 mg/d were started and the fever disappeared within 4 days. The patient remained well without relapse after 19 months of follow-up.

# RESULTS

A review of the medical literature identified 68 cases of HIV-associated histoplasmosis reported in Europe[1–6,8,10–15,18–20,22–25,29–34,36,42,43,45–47,50,53,55,56,61,62,64,66–69,71,75,76,80–82,88,89], to which we contribute 4 new patients, bringing the total to 72.

## Background

Selected features of all 72 patients are summarized in Table 1. There were 56 men (77.8%), and the median age of the patients was 35 years (range, 24–65 yr). Thirty-three patients were white, 29 black, 4 Hispanic and 2 Asian; the race of 4 patients was not reported.

The countries reporting cases of AIDS-associated histoplasmosis were Italy (20 cases)[3,5,6,14,20,30–32,53,56,68,81,

| Histopathology | Culture | Treatment Induction, Total Dose or Daily Dose | Outcome |
|---|---|---|---|
| BM: *Hcu* | - | AMFB+ itraconazole, NR | Alive 14 mo after diagnosis |
| Ln (abdominal): *Hcc* | - | AMFB, NR | Alive 10 mo after diagnosis |
| Colon resection: *Hcc* (postmortem) | - | NT | Died after surgery (ileocolectomy) |
| BAL, colon: *Hcc* | BAL, colon: *Hcc* | AMFB, 1400 mg | Relapse 3 mo after diagnosis; died 6 mo after diagnosis |
| Colon, Ln: *Hcc* | BAL, Ln: *Hcc* | AMFB, 1400 mg | Relapse 10 mo after diagnosis; died 11 mo after diagnosis |
| BM, CSF, Ln: *Hcc* | BM, blood, CSF: *Hcc* | Itraconazole 400 mg/d | Relapse 4 mo after diagnosis; 2nd relapse 2 mo later; died 8 mo after diagnosis |
| Gingival, Ln: *Hcc* | Gingival : *Hcc* | Itraconazole 400 mg/d | Alive 18 mo after diagnosis |
| BAL: *Hcc* | BAL: *Hcc* | Itraconazole 400 mg/d | Alive 3 mo after diagnosis |
| Skin, bone: *Hcc* | Skin, bone: *Hcc* | Itraconazole 200 mg/d | Died in a road accident 6 mo after diagnosis |
| Autopsy: L, li, Ln: *Hcc* | Negative | NT | Died 19 d after hospitalization |
| Skin, BAL: *Hcc* | Blood, skin: *Hcc* | ABCD 5 mg/kg per d → itraconazole 400 mg/d | Relapse 12 mo after diagnosis |
| Autopsy: skin, stomach, li, S, Ln, K, CNS, ht, adrenal glands, ovary, uterus: *Hcc* | Negative | NT | Died 8 d after hospitalization |
| BM: *Hcd* | Negative | Itraconazole 400 mg/d | Alive 9 mo after diagnosis |

present report [PR]; France (13 cases)[23,43,46,47,50,61,80]; Spain (13 cases)[1,4,10,11,22,24,64,69,71]; Germany (10 cases)[12,13,36,66,67,73,75,88]; Switzerland (6 cases)[15,25,29,42,45]; Belgium (5 cases)[8,18,62], the United Kingdom (2 cases)[82,89], and 1 case each from Norway[55], Portugal[34], and Denmark[76]. Apart from 4 African patients with HIV-2 infection[10,29,34,46], HIV-1 infection was diagnosed in all cases.

All but 7 cases were classified as imported histoplasmosis; autochthonous cases were observed in Italy (4 cases)[5,6,14,32], Spain (2 cases)[1,71], and Germany (1 case)[36]. The imported cases included 28 from South America[3,4,6,10,11,20,22,24,30–32,43,45,47,56,61,62,64,66,69,71,75,76,80,89,PR]; 27 from Africa[8,10,12,13,15,18,25,29,31,33,34,42,46,47,50,53,62,68,73,80,82,PR]; 4 from the United States[67,75,81,88]; 2 from Southeast Asia[23,55]. In 1 case the patient had traveled in both Central America and Africa[11], and another patient had traveled in both Africa and India[32]. In 1 case no mention was made of travel in endemic areas[2]. A median time interval of 24 months (range, 1–144 mo) elapsed between the last exposure of patients (travelers or immigrants) to endemic areas and the onset of PDH in Europe.

A previous diagnosis of AIDS had been made in 25 patients (34.7%)[3,6,10,11,13,20,23,25,31,43,46,47,50,66–68,75,80,89,PR], while PDH was the AIDS-presenting illness in 44 patients (65.6%)[2,4,5,8,12,14,15,18,24,30,32,42,45–47,53,55,61,62,68,73,75,80,88,PR]. Of those with prior AIDS and PDH, 11 had a concomitant opportunistic infection or AIDS-defining condition: 6 had Kaposi sarcoma, 2 had *Mycobacterium avium* complex (MAC) disease and CMV retinitis; and 1 each had *Pneumocystis* pneumonia (PCP), esophageal candidiasis, pulmonary tuberculosis and visceral leishmaniasis[3,10,23,25,46,47,50,66,76,PR]. Other major opportunistic infections were diagnosed in 7 patients: MAC disease in 3 and AIDS-dementia complex, PCP, pulmonary tuberculosis, and CMV in 1 patient each[10,18,22,30,56,82,PR].

At the time of the diagnosis of PDH, or during the last hospitalization of the patients with a postmortem

diagnosis, the median CD4 T-cell count was 20/μL (range, 0–352/μL).

A diagnosis of PDH was made during life in 63 cases (87.5%). Of the 9 cases with a postmortem diagnosis[5,10,30,56,80,PR], 3 had a positive blood culture first reported after death[25,30,56] and 6 were identified at autopsy.

## Clinical Manifestations

Widespread disseminated disease was noted in 66 cases (91.6%) and localized disease in 6 (8.3%). The site of involvement in the localized cases was the skin[18,23,29,31,36,53] in all but 1 case[82]. Overall skin involvement was reported in 34 of 72 patients (47.2%), with a similar prevalence in those acquiring the disease in Africa (12/27, 44.4%)[18,29,31,42,46,47,53,68,73] or in South America (13/28, 46.4%)[3,10,11,20,22,24,31,64,89,PR]. Skin lesions were most commonly described as papular (13 cases)[3,5,6,10,14,20,22–24,32,47,53,68] or maculopapular (8 cases)[1,10,42,47,64,PR] sometimes with ulceration and crusting (7 cases)[3,5,10,23,32,53,73]; nodular[11,29,32,46], pustular[55], or umbilicated[31] lesions were less common. Skin lesions were widespread (involving face, trunk, arms, and legs) in 22 patients and localized in 10 patients. In 2 cases the type of lesions and the location was not reported[4,75]. Six patients had concomitant oral ulcers[5,10,31,47,82,89].

Most patients (63/72; 87.5%) were febrile, and weight loss was described in 31 patients (41.6%) (Table 2). Complaints of lung involvement (cough, dyspnea, chest pain, hemoptysis) were observed in 21 cases (29.1%). Other common findings included hepatomegaly in 30 (41.6%), splenomegaly in 27 (37.5%), lymphadenopathy in 20 (27.8%), and diarrhea in 15 (20.8%). A chest radiogram was reported in 53 cases: a reticulonodular or interstitial pattern was observed in 28 cases (52.8%)[2,5,6,20,22–25,32,46,47,56,64,66–69,80,88,PR] and was associated with mediastinal adenopathy in 3[14,31,32]. Localized pulmonary infiltrates were observed in 7 cases; a cavitary lesion in 1, and 16 patients had a normal pattern (30.7%). Hematologic alterations were observed in 46 of the 52 patients for whom such data were available; pancytopenia was the most frequent (23/46, 50%)[5–7,10,14,15,20,23,30,46,47,56,61,66,71,75,81,PR] followed by anemia alone (6 cases)[11,18,34,73,PR] or associated with leukopenia (9 cases)[3,10,13,42,43,82,88], leucocytosis (1 case)[PR], or thrombocytopenia (2 cases)[11,31]; 4 patients had leukopenia[32,46,76] and 1 had leukopenia associated with thrombocytopenia[47]. Among patients with PDH caused by *Hcc*, 6 of 65 (9.2%) presented with a sepsis-like picture with multiorgan failure [5,20,25,46,56,PR].

The 7 patients infected with *Hcd*[8,15,29,34,42,62,PR] presented with a febrile syndrome in all but 1 case, associated with weight loss (4 cases), lymphadenopathy (3 cases), splenomegaly (3 cases), hepatomegaly (2 cases), skin lesions (2 cases), and diarrhea (2 cases). Three patients had pancytopenia, 2 anemia, and 1 developed a picture of sepsis-like syndrome.

## Microbiologic Diagnosis

A diagnosis during life was made by histopathology plus a positive culture in 44 patients (2 of whom also had positive polymerase chain reaction [PCR]) (69.8%)[1–6,8,10,11,13–15,20,22–24,29–33,36,42,47,53,55,62,64,66,67,69,73,80–82,88,89,PR]; histopathology in 18 (plus PCR in 1 case) (28.6%)[12,18,25,34,43–46,50,61,68,71,75,76,PR]; and culture in 1[32]. Organisms resembling *Hcc* were seen on peripheral blood smears in 3 cases[25,46,55]. Of note is that in no case was the diagnosis based on antigen detection or serology.

As shown in Table 3, the fungus was cultured from 72 specimens and demonstrated by means of histopathology of 85 specimens; the specimens from which the diagnosis was established most frequently were skin, bone marrow, and blood. Based on culture and/or histopathology, *Hcc* was identified in 65 cases (90.3%). In Africa all the cases but 1 (coming from Zimbabwe) were acquired in the central and western part of the continent (Figure 3), and *Hcc* was the species largely identified (20 cases, 74%).

## Treatment and Outcome

Ten patients (9 with a postmortem diagnosis) were not treated[1,6,10,12,25,56,80,PR], and therapy was not reported for 2 patients[36,68] (see Table 1). Antifungal induction therapy was started in 59 patients: 26 received amphotericin B (44%)[2,4,8,11,13,22–24,32,33,45,47,50,55,62,64,66,69,71,76,80], mainly in the deoxycholate formulation; 6 received combination antifungal therapy consisting of amphotericin B plus itraconazole (5 patients)[5,46,73,75], or flucytosine (1 patient)[67]; and 7 were treated with a sequential therapy (amphotericin B followed by itraconazole)[6,11,14,15,42,46,PR]. Eighteen patients were treated with oral itraconazole (30.5%)[3,11,18,29,31–32,34,43,46,53,61,81,82,88,89,PR], 400 mg daily in most, and 3 received fluconazole[18,20,30]. The mortality rate during the induction phase of treatment was 15.2% (9/59): 4 of 22 (18.2%) in the amphotericin B group, 1 of 16 (6.2%) in the itraconazole group, 2 of 3 (67%) in the fluconazole group, and 2 of 6 (33.3%) in the combination group (amphotericin B plus itraconazole).

Chronic suppressive therapy with itraconazole was used for 32 patients[2–4,6,10,11,14,15,18,22,31,33,34,42,43,45–47,61,66,67,69,71,80,81,89,PR], ketoconazole[47,62] and amphotericin B (subsequently switched to itraconazole) in 2[45,80], and fluconazole in 1[76].

Of the 64 patients in whom the outcome was known, 37 (57.8%) died[1,3,5,6,8,10,12,18,20,22–25,30,32,46,47,56,61,67,69,73,75,80,81,89,PR]. Eighteen (28.1%) patients died within 30 days of diagnosis, regardless of treatment[1,5,8,10,12,20,23–25,30,46,73,PR], and 19 died a median of 8.5 months after diagnosis (range, 1–24 mo). Seven patients (17.5%) relapsed a median of 4 months after diagnosis (range, 2–12 mo)[31,67,80–81,PR] 3 of whom had discontinued therapy[42,67,PR].

## Autopsy Findings

Autopsy data are available for 13 cases[5,6,10,12,18,20,24,73,PR]: the most frequently involved organ was the lung in 12 cases[5,6,10,12,18,20,24,72,PR]; followed by spleen in 11[5,6,10,12,18,20,24,72,PR]; liver in 8[5,6,10,12,24,PR]; lymph nodes in 7[5,6,10,12,24,PR]; bone marrow in 4[10,12,18,20]; and skin in 2[5,PR]. A median of 4.5 organs per patient (range, 1–11)

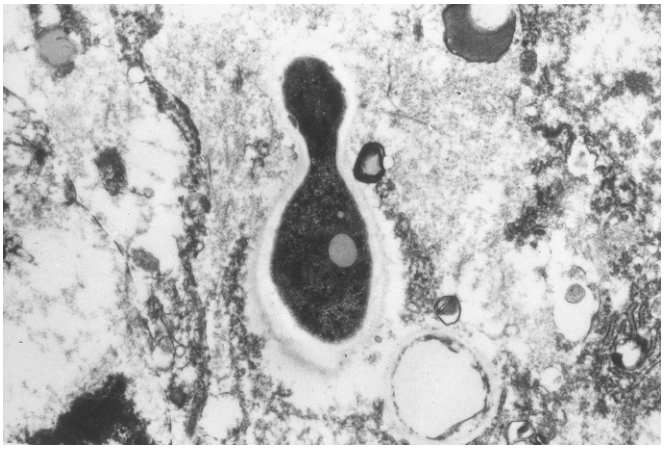

**FIGURE 1.** Lung autopsy (Patient 71, Table 1), electron micrograph: a yeast cell (*Histoplasma capsulatum* var. *capsulatum*) with a budding process (silver impregnation, original magnification × 7000).

were involved. In no case was histoplasmosis considered to be an incidental finding at autopsy except for a patient with presumed colon malignancy who died during surgery and in whom *Hcc* was disclosed in the colonic lesion[80].

## DISCUSSION

Histoplasmosis is a common opportunistic mycosis among HIV-infected individuals living in geographic areas where *H. capsulatum* is endemic. There are 2 recognized human pathogenic variants of *Histoplasma*: *Hcc*, which is endemic in the United States, Central and South America, and some parts of tropical Africa (including Zimbabwe and South Africa), and *Hcd*, which has been reported exclusively in Western and Central Africa (Senegal, Mali, Burkina Faso, Ivory Coast, Chad, Congo, the Democratic Republic of Congo, Nigeria) and Madagascar. Most of the information regarding HIV-associated histoplasmosis is found in reports from the United States and South America, which show some clinically significant differences in the modality of presentation[21,39–41,46,63,72,79]. In Europe, HIV-associated histoplasmosis is rarely encountered, and in most cases is an imported disease described as a single case report or in a small series of patients. A retrospective-prospective survey of histoplasmosis in Europe conducted by the European Confederation of Medical Mycology between January 1995 and December 1999 identified a total of 131 cases from 18 participating countries with 3 countries (Italy, Germany, the United Kingdom) reporting more than 20 cases[9]. AIDS was the most frequently reported underlying disease (38/98, 38.7% of the cases for whom complete information was available).

This review of 72 patients with HIV-associated histoplasmosis recorded in 10 European countries over 20 years includes 7 autochthonous cases (9.7%), most of which were observed in Italy[5,6,14,32]. The other 65 cases are a blend of imported cases acquired in endemic areas of Africa, South America, and the United States. In this retrospective experience PDH was diagnosed after a median interval of 24 months between last residence in or travel to endemic areas and arrival in Europe; this finding is consistent with previous studies conducted outside endemic areas that have suggested a reactivation of a latent infection rather than an exogenous acute infection as the main pathogenetic mechanism of disease[51,70].

As far as autochthonous cases are concerned, it should be noted that studies carried out in Italy during the 1960s and 1970s showed the isolation of *Hcc* from soil and animals[57,77]; furthermore, an epidemiologic survey in Italy using the histoplasmin skin test demonstrated positivity in nearly 1% of the general population living along the River Po[78], a finding that was later confirmed in a young student population living in the same area[19]. For comparison, in the highly endemic areas of the United States (Indiana, Ohio, Illinois, Kentucky, Tennessee, and Missouri) 80%–90% of the population had a positive histoplasmin skin test[28].

Apart from the existence of microfoci of *H. capsulatum* outside the known endemic areas, the possibility of importing this fungus to Europe by means of contaminated soil used for farming deserves further study[36].

Seven of the cases of *Hcd* (6 of which were previously reported) were observed in patients living in or coming from the Democratic Republic of Congo (formerly Zaire), Cameroon, Congo, Nigeria, Liberia, Guinea-Bissau, and the Ivory Coast[8,15,29,34,42,62,PR]. The African form of histoplasmosis (*Hcd*) that usually manifests as localized lesions of the skin and bone, has rarely been reported in the setting of HIV infection[17,35,37]; excluding the patients with a diagnosis made in Europe and included in this review, we are aware of only 5 previously reported cases[17,35,37,59]. However, it is unclear whether this is due to a truly low incidence of the disease or whether it is a problem of under-reporting

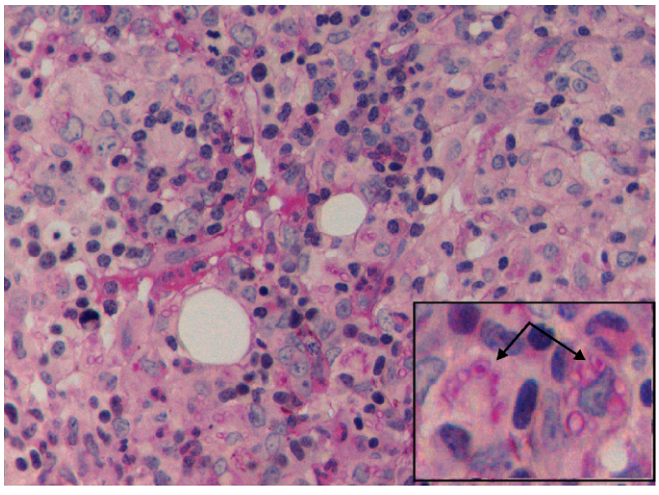

**FIGURE 2.** Bone marrow section (Patient 72, Table 1) showing periodic acid-Schiff (PAS)-positive intracytoplasmic aggregates of ovoid yeast forms (diameter 15 μm) morphologically compatible with *Histoplasma capsulatum* var. *duboisii* (original magnification × 400). Inset, at higher magnification: cluster of yeast cells localized in the cytoplasm of macrophages (arrow) (× 800).

**TABLE 2.** Characteristics of 72 HIV-Infected Patients With Histoplasmosis Reported in Europe

| Characteristic | Value |
|---|---|
| Median age, yr (range) | 35 (24–65) |
| Male (%) | 56 (78) |
| Risk factor for HIV infection (%) | |
| Heterosexual | 34 (47) |
| Homosexual or bisexual | 15 (21) |
| Intravenous drug abuser | 10 (14) |
| Unknown or not reported | 13 (18) |
| Median CD4 cell count, cells/μL (range) | 20 (0–352) |
| PDH diagnosis (%) | 63 (87) |
| PDH as AIDS-defining illness (%) | 44 (61) |
| HAART at time of diagnosis* | 3 (4) |
| Predominant clinical manifestation | |
| Fever | 63 (87) |
| Weight loss | 31 (42) |
| Hepatomegaly | 30 (41) |
| Splenomegaly | 27 (37) |
| Lymphadenopathy | 20 (28) |
| Diarrhea | 15 (21) |
| Pancytopenia | 23 (50)† |
| Treatment | |
| Amphotericin B‡ | 26 (44) |
| Itraconazole | 18 (30) |
| Fluconazole | 3 (5) |
| Combination (amphotericin B + itraconazole)§ | 6 (10) |
| Sequential (ampothericin B followed by itraconazole) | 7 (12) |
| Untreated or not reported | 12 (17) |
| Outcome | |
| Early mortality | 18 (28.1) |
| Late mortality | 19 (32.8) |
| Survived | 27 (42.2) |
| Relapse | 7 (17.5)‖ |

Abbreviations: PDH = progressive disseminated histoplasmosis; HAART = highly active antiretroviral therapy.

*All patients at the time of diagnosis of PDH had low adherence to the therapeutic regimen.

†Percentage calculated on 46 patients.

‡Including liposomic amphotericins.

§Including 1 patient treated with amphotericin B and flucytosine.

‖Percentage calculated on 40 patients.

or under-recognition (it is worth noting that a recent review of opportunistic infections in HIV-infected patients in sub-Saharan Africa makes no mention of histoplasmosis)[44]. It has been suggested that this rarity may be due to the lack of overlap in the distribution of the 2 diseases: HIV is predominantly urban, whereas the African form of histoplasmosis is rural[35]; however, as reported in a small series of patients from the Congo, PDH was initially mistaken for tuberculosis thus confirming the hypothesis of an under-recognized disease[17]. An interesting finding of our study was the observation that *Hcc* is the species more frequently involved in cases of AIDS-associated PDH also in Africa, despite the fact that the designation ''African histoplasmosis'' refers to *Hcd*.

Histoplasmosis was the AIDS-defining disease in nearly 61% of the patients considered here (44/72), a result higher than that observed in the United States series[40,48,72,74,84,86] but in line with those from Central and South America[21,39,49,63] (Table 4). However, patients with AIDS-associated histoplasmosis diagnosed in Europe also developed the illness in an advanced stage of disease with a very low median CD4+ cell count (see Table 4). Unlike people who are not immunocompromised (who rarely develop disseminated disease), patients with AIDS usually present PDH, a finding that was also observed in 92% of the patients in the present series; localized disease presented exclusively with skin or oral involvement in 8.3% of cases. Interestingly, it has recently been reported that skin involvement is significantly more common in Brazilian[49] and Argentinian patients[63] (66% and 75% of cases, respectively) than in previously published United States cohorts (4%–25% of cases)[48,49,74,84]: this finding is confirmed by our analysis showing overall skin involvement in 47% of the cases reported in Europe. Furthermore, we could also verify the rate of skin involvement in patients acquiring the disease in Africa or South America, and found that the occurrence of skin lesions was quite similar (44.4% vs. 46.4%) in the 2 groups. Clinically a variety of skin lesions was described, the most common being papular or maculopapular manifestations that sometimes were ulcerated or had crusting. However, not only skin lesions with a range of morphologic appearances were observed in different patients, but also lesions characterized by varying morphology were identified in the same patients in 8 cases[5,10,14,23,32,53,73,PR].

A 2001 analysis of patients with AIDS-associated histoplasmosis in Zimbabwe showed that 46% of the cases had cutaneous lesions, which is in agreement with our findings[38]. However, it is worth noting that only 11 (13.5%) of a recent series of AIDS patients with histoplasmosis from French Guyana[21] and 18 (17.3%) from Panama had cutaneous/mucosal involvement[39].

Based on restriction fragment length polymorphism (RFLP) and random amplification of polymorphic DNA (RAPD) analyses, it has been suggested that the clinical differences in the presentation of histoplasmosis in patients with AIDS in the United States and Brazil are due to a distinct genetic diversity of the organism involved[49], and experimental infections in animal models conducted with different representative strains seem to confirm the existence of pathogenic differences. The same may be true (at least speculatively) in the case of patients with histoplasmosis acquired in Africa. Interestingly, a different organ tropism has been observed in the different species of *Cryptococcus neoformans*, with a more frequent association between skin involvement and serotype D infection[26,79].

Because the clinical manifestations of PDH are not specific, the disease may be easily overlooked in a nonendemic area; since immigration from endemic areas is an increasing phenomenon, physicians in Europe need to be familiar with this opportunistic infection. Intestinal involvement

**TABLE 3.** Methods of Diagnosis of HIV-Associated Histoplasmosis Reported in Europe

| Specimen | Positive Cultures (No.) | Positive Histopathology (No.) | Positive PCR (No.) |
|---|---|---|---|
| Blood | 20* | 3 | ND |
| Bone | 1 | 1 | ND |
| Bone marrow | 11† | 21† | ND |
| Bronchoalveolar lavage | 6 | 7 | 1 |
| Cerebrospinal fluid | 3 | 1 | ND |
| Intestine | 1 | 7^ | ND |
| Liver | - | 1 | ND |
| Lung | - | 1 | ND |
| Lymph node | 3‡ | 12‡ | ND |
| Oral mucosa | 2 | - | ND |
| Skin | 22§ | 30§ | 3 |
| Sputum | 1 | 1 | 1 |
| Urine | 2 | - | ND |
| Total | 72 | 85 | 5 |

Abbreviations: PCR = polymerase chain reaction (references 31, 53, 66, 68); ND = not done.
*Two *H. capsulatum* var. *duboisii*.
†Three *H. capsulatum* var. *duboisii*;
^One *H. capsulatum* var. *duboisii*.
‡One *H. capsulatum* var. *duboisii.*
§Two *H. capsulatum* var. *duboisii*.

presenting with abdominal pain and ulcerated or polypoid lesions revealed by colonoscopy or during surgical resection was documented in 8 patients (11%)[13,34,43,46,61,80]; however, 23 patients (32%) had gastrointestinal complaints[8,11–13,18,20,22,24,34,43,45-47,61,67,69,75,80,81,88,PR]. Once again, gastrointestinal involvement seems to be more common in this European study (which included mixed African and South American patients) than in North American patients. Interestingly, in a case-control study, univariate analysis showed that the presence of gastrointestinal lesions was 1 of the variables associated with an increased risk of a poor outcome, although this was not confirmed by multivariable analysis[41]. In a pathologic study of 53 patients with gastrointestinal and hepatic histoplasmosis, the most frequently involved locations were the small bowel (79%) and large bowel (55%)[52].

A sepsis-like syndrome in patients with AIDS-associated PDH was described by Wheat and Small[83] in 1984 in approximately 10% of cases: we found a similar prevalence among patients with *Hcc* (6/65, 9.7%) in our review of European patients[1,5–6,12,15,20,54].

Central nervous system involvement (as a manifestation of disseminated disease or as an isolated focal infection) was infrequent (5/72 patients, 6.9%)[1,4,10,81,PR], in line with previous reports from Texas (7.8%) and Indiana (4.2%)[72,84].

The initial chest radiogram had a reticulonodular or interstitial pattern in nearly one-half of the patients, and a

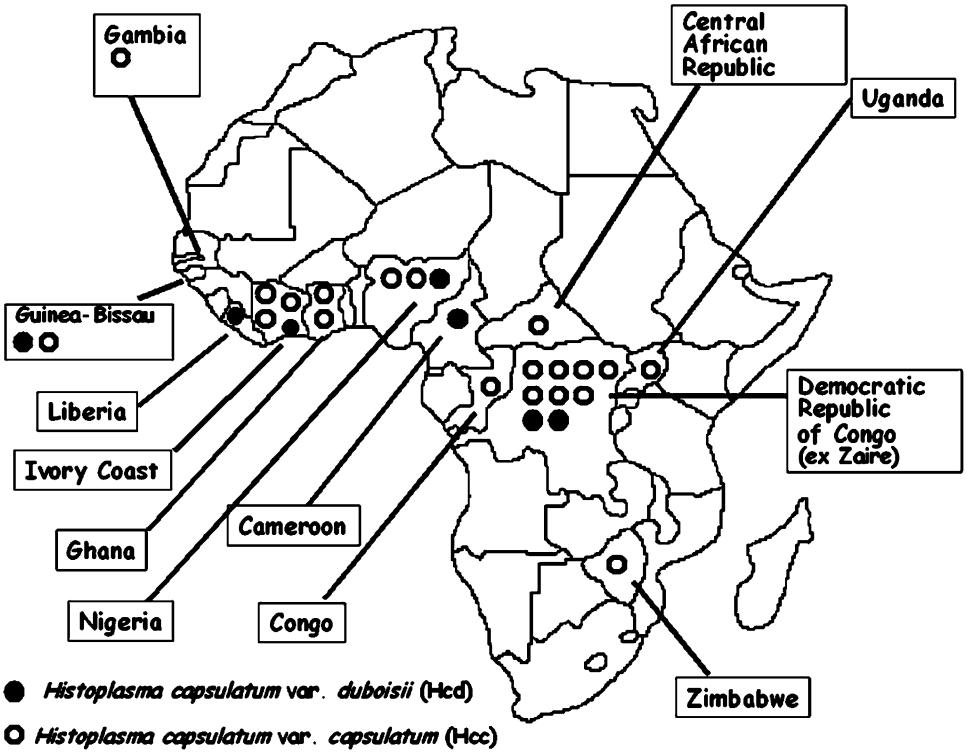


**FIGURE 3.** Map of Africa showing the distribution of countries of origin of patients with *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii* diagnosed in Europe.

**TABLE 4.** Demographic and Clinical Features in Patients With HIV-Associated Histoplasmosis, Previous and Present Reports

| Variable | United States (Refs. 40, 48, 72, 74, 84, 86) (n = 476) | Central America And South America (Refs. 21, 39, 49, 63) (n = 231) | Africa (Refs. 38, 65) (n = 71) | Europe (Ref. 54) (n = 51) | PR (n = 72) |
|---|---|---|---|---|---|
| Median age, yr (range) | NR (19–74) | NR (15–47) | 37 (30–54) | 37 (24–54) | 35 (24–65) |
| Male (%) | 311/340 (91.5) | 185 (80,1) | 16 (61.5) | NR | 56 (77.8) |
| Median CD4 cell count, cells/μL (range) | 18–32 (0–638) | 44–45 (4–297) 65 (2–428) | NR | 20 (0–260) | 20 (0–352) |
| AIDS defining (%) | 88/216 (41) | 83/120 (69.2) | (100) | 27 (53) | 44 (61.1) |
| Skin involvement (%) | 28/476 (6) | 60 (26) | 40/71 (56)* | 26 (51) | 34 (47.2) |
| Pulmonary involvement (%) | 244/471 (52) | 128 (55.4) | (50) | 29 (57) | 37/53 (70) |
| Brain/meningeal involvement | 18/402 (4.5) | 5/45 (11.1) | NR | 13 (25.5) | 5 (6.9) |
| Positive cultures | 187/266 (70.3) | 179 (77.5) | NR | 37 (72) | 47 (65.3) |
| Positive blood cultures | 166/299 (55.5) | 73/120 (60.8) | NR | 12 (44) | 20 |
| GI involvement | 20/340 (5.8) | 64/149 (42.9) | (33) | 16 (31.4) | 23 (32) |
| Relapse rate | 4/21 (19) | 11/120 (9.2) | NR | 9 (17.6) | 7/40 (17.5) |

*One work described only cases of disseminated cutaneous histoplasmosis.

normal pattern in one-third: this finding is in keeping with the results observed in a cumulative series of 214 patients[72].

In this European retrospective experience, the diagnosis of histoplasmosis was made during life by means of culture and histopathology in the majority of cases (68%); overall cultures were positive in 65% of cases, with skin, blood, and bone marrow proving to be the specimens most useful to make a diagnosis. These results are in agreement with those previously reported in the literature. However, a rapid diagnostic test is needed since cultures may take up to 2 weeks to become positive and histology is not always available. In this regard it should be noted that a histoplasma antigen test (available only in the United States) showed a sensitivity of 95% and 86%, respectively, in urine and serum for the diagnosis of PDH among AIDS patients[87]. Interestingly an interlaboratory comparative study recently conducted at the Statens Serum Institute of Copenhagen showed an excellent correlation with the results obtained at the reference center in the United States, and we hope in the future it may be available to the European medical community[7]. Finally, the feasibility of using PCR for the rapid diagnosis of histoplasmosis has been evaluated in a few cases in Europe[31,53,66,68], but further studies are necessary, especially to establish the best target for its use.

Amphotericin B desoxycholate (44%) and itraconazole (30%) were the single most frequently used drugs for the treatment of patients with HIV-associated histoplasmosis diagnosed in Europe. The mortality rate during induction therapy was 15%, and there was a cumulative response rate of 60% (based on patient survival), but the nature of this study (a review of case reports published over 20 years) with several possible biases (such as the severity of the disease or differences in the dosages used) does not allow any conclusion concerning treatment efficacy. Both drugs have been considered to be better than fluconazole in the treatment of histoplasmosis in patients with AIDS. It is perhaps also worth noting that a randomized, double-blind comparative trial conducted in the United States showed a better outcome in patients with moderate-severe AIDS-associated histoplasmosis treated with liposomal amphotericin B than in the patients receiving the desoxycholate formulation[48].

Autopsy data relating to 13 patients showed disseminated disease in the majority of cases (83%), with a median of 4.5 organs involved per patient; the most frequently involved organs were the lungs, spleen, liver, and lymph nodes, as also observed by Markowitz et al[58] in an autopsy survey carried out in an inner-New York City AIDS population. *H. capsulatum*, together with CMV, *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, and MAC, seems to be 1 of the opportunistic infections that is more likely to disseminate in the absence of a valid cell-mediated immune response.

In conclusion, PDH is unusual in Europe but may increase with the expansion of immigration from endemic areas and should be included in the differential diagnosis of opportunistic infections in HIV-positive patients especially if they are coming or returning from endemic areas. Physicians in Europe must become more familiar with the clinical findings and diagnostic approach in order to improve the outcome by earlier therapy.

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