Case Report: Imported African Histoplasmosis in an Immunocompetent Patient
40 Years after Staying in a Disease-Endemic Area

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Abstract. Histoplasmosis caused by Histoplasma capsulatum var. duboisi is a rare disease outside central and western Africa. In Europe, all cases are imported. We report a case of an African histoplasmosis with isolated pulmonary involvement in a non-immunocompromised patient that occurred 40 years after his stay in a disease-endemic area. The patient was given itraconazole. 18F-fluoro-2-deoxy-D-glucose positron emission tomography–computed tomography was used to assess evolution during treatment. The outcome for the patient was favorable.

African histoplasmosis may occur in persons without identified immunodeficiency, even a long time after exposure. African histoplasmosis caused by Histoplasma capsulatum var. duboisi, a dimorphic fungus, is an invasive fungal disease endemic to central and western Africa and Madagascar. About thirty cases were reported in Europe and all are imported were cases.1–8 We report an immunocompetent Caucasian patient without identified immunodeficiency who had chronic pulmonary African histoplasmosis diagnosed four decades after a stay in western Africa.

A 60-year-old man from Portugal was admitted to an emergency department in October 2006 for cough with clear sputum and chest pain. His medical history indicated a gastrroduodenal ulcer. He still visited his native country each year even though he had lived in France for 40 years. Forty years ago, he lived in Guinea-Bissau for two years during his military service. He is now a factory worker and enjoys gardening.

The functional pulmonary symptoms occurred gradually without chills, sweats or fever for several weeks. Results of a clinical examination were normal. Oxygen saturation was 96%, temperature was 37°C, and there was no weight loss. A chest radiograph showed bilateral diffuse opacities with nodular cavi-

Laboratory tests showed normal blood cell counts: 5,400 leukocytes/mm³ with 3,400 neutrophils/mm³, 1,400 lymphocytes/mm³, and 200 eosinophils/mm³. The C-reactive protein level was 138 mg/L, and serum levels of liver enzymes, bilirubin, and lactate dehydrogenase were within reference ranges. Sputum cultures were negative for bacteria, mycobacteria, and fungi. Serologic test results for aspergillosis and hydatidosis were negative. Abdominal and cardiac ultrasound and bronchoscopic evaluations show normal results. Bronchoalveolar lavage fluid contained 223 \times 10³ cells/mL, 93% alveolar macrophages, 5% lymphocytes, 2% neutrophils, and no neoplastic cells. Specific staining and/or cultures were negative for Pneumocystis jirovecii, mycobacteria, and bacterial microorganisms. Gomori-Grocott staining showed oval-shaped yeast 8–10 μm in diameter with narrow budding compatible with H. capsulatum var. duboisi (Figure 2). The culture yielded growth of a mycelial phase with tuberculate macroconidia that was visible after lactophenol staining. Moreover, a serologic test result was also positive for histoplasmosis (arc M).

A biopsy specimen of a right pulmonary nodule showed granuloma and suppuration and evidence of the same microorganisms after hematoxylin and Grocott staining. Initial 18F-fluoro-2-deoxy-D-glucose positron emission tomography–computed tomography (PET-CT) showed exclusive uptake by lung lesions and a maximum standardized uptake value (SUVMmax) of 8.4 mGy (Figure 3).

Screening results for an innate or acquired immunodeficiency were negative, except for a slightly reduced CD4 cell count of 480 cells/mm³ (reference range = 500–1,500 cells/ mm³) and a CD8 cell count of 216 cells/mm³ (reference range = 300–900 cells/mm³) compared with a normal CD56 cell count of 216 cells/mm³ (reference range = 100–350 cells/mm³). During treatment, CD4 and CD8 cell counts returned to reference levels. Serum protein electrophoresis and immunoel ectrophoresis showed normal results, and IgA, IgG, and IgM levels were normal. Serologic results for infection with human immunodeficiency virus (HIV) were negative. Production of interferon-γ (INF-γ) or interleukin-12 (IL-12)p40 in response to bacillus Calmette Guérin (alone or with INF-γ or IL-12) was normal, excluding a genetic defect in the IL-12/INF-γ axis or auto-antibodies against IFN-γ. The T cell lymphocyte in vitro proliferative responses to mitogen and antigens were normal. Antinuclear antibodies and cytoplasmic antibodies against neutrophils were absent. No iron overload was detected (transferrin saturation rate = 23%).

The patient was treated orally with itraconazole (600 mg/day for 3 days, then 400 mg/day). Plasma drug levels were carefully monitored: peak levels for hydroxyl-itraconazole and itraconazole ranged from 1,900 to 3,000 μg/mL and from 1,560 to 3,000 μg/mL, respectively (reference values < 2,000 μg/mL for itraconazole and < 6,000 μg/mL for hydroxyl-itraconazole). Residual levels for itraconazole ranged from 1,053 to

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2,065 μg/mL (reference value £ 250 μg/mL). Initial respiratory symptoms resolved in less than six months.

Although the patient is now healthy and has not showed any respiratory symptoms after seven years of treatment, sequential annual chest CT did not show any improvement. Multiple excavated nodules, some calcified, persisted although bronchoalveolar lavage fluid was sterile four years after initiation of treatment. A PET-CT performed after more than seven years of well-observed treatment, with careful screening for plasma concentrations, showed a decrease, but not an extinction, in uptake by lung nodules (SUVmax = 4.6 mGy). We then decided to stop antifungal treatment but continued clinical and radiologic monitoring. Six months after treatment was stopped, no symptoms were observed.

We describe a clinical case of histoplasmosis with localized pulmonary involvement caused by *H. capsulatum* var. *duboisii* that occurred 40 years after exposure. African histoplasmosis is caused by *H. capsulatum* var. *duboisii*. The exact pathogenesis remains unclear. The usual routes of acquisition are believed to be airborne contamination from soil and rarely by direct inoculation. However, the most frequent radiologic findings for the lungs are either miliary or calcified parenchymal nodules, which suggest hematogeneous or lymphatic spreading.9,10 Two forms of African histoplasmosis are typically described: a localized chronic form that involves skin, subcutaneous tissue, bones, or lymph nodes; and a disseminated rapidly evolving form, which can also involve the spleen, liver, lungs, and abdominal viscera through ematogeneous invasion.9 For the patient in this study, we suggest a chronic pulmonary form, as described for infection with *H. capsulatum* var. *capsulatum*, because he had a persistent productive cough and cavitary disease, and *H. capsulatum* var *duboisii* was isolated from this patient. This clinical feature is not a classical picture for infection with *H. capsulatum* var. *duboisii*. In contrast to histoplasmosis caused by *H. capsulatum*, exclusive lung involvement seems to be rare with infection with *H. capsulatum* var. *duboisii*, as observed for our patient.1,11–13

*Histoplasma capsulatum* var. *duboisii* infections have been reported mainly in patients not infected with HIV; 17 cases were reported in Europe during 1980–1994, only 3 of these patients infected with HIV, and no other underlying immunodeficiency was described. Nevertheless, all three patients had disseminated disease in comparison with only one patient not infected with HIV.4 In contrast, *H. capsulatum* var. *capsulatum* infections are clearly related to a cellular immunodeficiency, especially for disseminated disease. Thus, in areas to which this organism is highly endemic, it remains the main acquired immunodeficiency syndrome–defining disease.14–16 In the present case, we did not find evidence of any underlying chronic pulmonary disease (including vasculitis associated with cytoplasmic antibodies against neutrophils) or underlying immunodeficiency. One may hypothesize that the natural history of such chronic pulmonary disease may be caused by association of a pulmonary inoculation and a progressive long-lasting local infection in a context of competent immune system that prevents dissemination associated with unusual fungal pathogen characteristics. As for tuberculosis, such chronic pulmonary features highlight the ability of *H. capsulatum* var. *duboisii* to produce latent infection in granuloma and local reactivation several years after initial infection.

Because histoplasmosis has only observed in persons from Europe who traveled to Africa or in persons born in Africa, invasive infection is believed to be caused by endogenous reactivation of a latent infection imported from disease-endemic countries. Time between infection and reactivation may be long, which would explain the cases reported several years after persons returned from Africa,17 as found with tuberculosis or cryptococcal disease (serotype B/C). An epidemiologic survey in Europe showed that for at least 25% of patients, symptoms did not occur for at least five years after travel.18 To the best of our knowledge, the present case is the...
most delayed diagnosis ever recorded for *H. capsulatum* var. *duboisii*, other than a case of *H. capsulatum* var. *capsulatum* lung reactivation reported 45 years after a person traveled to Africa. 19

Amphotericin B, a lipid formulation of amphotericin B, and itraconazole are the drugs of choice for treating *H. capsulatum* var. *capsulatum* infections. 2,20 These drugs are used to treat *H. capsulatum* var. *duboisii* infections because of the absence of specific guidelines for the management of such patients. Itraconazole appeared to be clinically efficient and cost-effective in the patient in this study. However, the persistence of radiologic and PET-CT lesions suggested a residual infection rather than scar lesions. We then decided to maintain antifungal therapy 21 until the patient appeared clinically cured and radiologic (chest CT and PET-CT) stability was assessed. Although rare, a diagnosis of African histoplasmosis should be kept in mind for persons born in Africa or for travelers to Africa, 22,23 even many years after their return from the disease-endemic area or if they do not show underlying immunosuppression. Because the exact duration of antifungal treatment is not known, we usually recommend prolonged therapy. However, PET-CT findings may improve monitoring and lead to a more precise therapeutic strategy.

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