Short Report: Serum Aspergillus Galactomannan for the Management of Disseminated Histoplasmosis in AIDS

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Abstract. Disseminated histoplasmosis is an emerging infection in patients with cellular immune deficiency in non-endemic countries, caused by the migration from endemic regions and the development of travels. Diagnosis can be challenging in this context because rapid diagnostic tools such as Histoplasma antigen detection or appropriate molecular tools are generally unavailable, serology is often negative in immunosuppressed patients, and isolation of the fungus from cultures often takes several weeks. Here, we report the contribution of galactomannan serum detection for the management of an HIV-infected patient with disseminated histoplasmosis.

INTRODUCTION
Histoplasmosis caused by Histoplasma capsulatum var. capsulatum is endemic in the United States, the Caribbean, and Central and South America and occurs with much less frequency in Africa and South East Asia. Disease can be caused by primary infection following airborne exposure or to reactivation of a latent infection. Histoplasmosis is the most frequently reported endemic mycosis in Europe and most cases occur in immunosuppressed patients, with a reactivation several years after the primary infection. Its diagnosis can be challenging, because serological methods based on specific antibody detection are usually not reliable in immunocompromised patients with histoplasmosis and Histoplasma antigen detection in blood, urine, and cerebrospinal fluid, which is a specific and sensitive assay for patients with disseminated disease, and is often unavailable in Europe.

Furthermore, immune reconstitution inflammatory syndrome (IRIS) can occur and its distinction with a relapse is not always easy. Interestingly, several authors have reported a non-specific positive Aspergillus galactomannan (GM) assay at the diagnosis in patients with culture-confirmed histoplasmosis. Here, we have studied the possible contribution of the GM assay, in comparison with Histoplasma antigen and 1,3-β-D-glucan (BG) detections, for the diagnosis of disseminated histoplasmosis and histoplasmosis-associated IRIS in a patient with acquired immunodeficiency syndrome (AIDS).

CASE REPORT
A 43-year-old woman was first admitted to our department in July 2010 for painful oral mucous ulcerations with gingival hemorrhage. She had been diagnosed with human immunodeficiency virus-1 (HIV-1) infection in 2003, during her fourth pregnancy. She discontinued antiretroviral therapy and was lost to follow-up until September 2009, when she first complained of oral mucous lesions. Several local therapies and a fluconazole oral regimen had shown no efficacy.

On physical examination at admission, she had mild fever (38.3°C), and palatine ulcerations were present. Fixed and rubbery cervical lymph nodes were found. Abdomen was soft on palpation without hepatosplenomegaly. Skin examination showed multiple facial nodular lesions. White blood cells count was 4,600/mm³ (67% neutrophils, 17% lymphocytes), hemoglobin level was 105 g/L, and platelet count was normal. Blood lactate dehydrogenase level was 798 IU/L (N < 460 IU/L). The CD4+ cell blood count was 50/mm³ (6%) and HIV-1 viral load was 7,700 copies/mL. The serum galactomannan (Platelia Aspergillus EIA, BioRad, Marnes la Coquette, France) was highly positive with an index of 28, (negative if the index value was < 0.5). Interestingly, BG (Fungitell assay) was also positive (252 pg/mL, negative when < 80), and Histoplasma antigen detected in serum (10 equine infectious anemia [EIA], positive when ≥ 3 EIA) at the French National Reference Center for Invasive Mycoses and Antifungals, Institut Pasteur, Paris (Alpha Histoplasma EIA test kit, IMMY laboratory). Chest and abdomen computed tomography were normal. Skin and oral mucous ulcerations biopsies and lymph node aspiration were performed and showed intra- and extra-cellular small yeasts. Cultures of the skin biopsies grew Histoplasma sp. The colonoscopy showed several ulcerations and histopathological analysis showed intracellular small yeasts compatible with H. capsulatum var. capsulatum.

She was treated with liposomal amphotericin B (3 mg/kg/d) for 14 days and then with itraconazole (200 mg orally twice daily), with rapid and major clinical improvement. The GM value, Histoplasma antigen, and BG decreased to 7.8, 5.5 EIA, and 194 pg/mL at Day 14, respectively, and GM to 6.6 at Month 1 (Figure 1). Combined antiretroviral therapy (cART) associating tenofovir, emtricitabine and raltegravir were initiated during hospitalization. After 3 weeks, HIV viral load was 139 copies/mL and CD4+ cell count was 69/mm³.

She was lost to follow-up for several weeks and discontinued her medications. Three months after discharge, HIV viral load was 430,289 copies/mL and CD4+ cell count had fallen to 42/mm³ (Figure 1).

Five months after the initial diagnosis of disseminated histoplasmosis, she was readmitted for swollen cervical bilateral lymph nodes, nausea, and diarrhea. Physical examination was otherwise unremarkable excepting a remaining nodular lesion on her chin. A novel lymph node biopsy showed numerous intracellular small yeasts on histological analysis. A tight stenosis of the ascending colon was found at endoscopy, with no fungus on biopsy examination. We first suspected a relapse and liposomal amphotericin B was restarted for 14 days with
only a mild decrease in the lymph nodes size. She had restarted cART a few weeks before admission and HIV viral load was down to 140 copies/mL and CD4+ cell count was 120/mm³ by this time. Fungal cultures of both lymph node and colon remained negative. In this context, an IRIS rather than a relapse was considered. The GM index had continued to decrease and was then at 0.59, Histoplasma antigen level was stable (6.1 EIA), reinforcing the diagnosis of IRIS. Note-worthy, BG was still >500 pg/mL at the time of IRIS. No anti-inflammatory treatment of IRIS was prescribed.

DISCUSSION

Diagnosis of histoplasmosis in HIV-infected patients in non-endemic areas can be challenging: isolation of Histoplasma from cultures is the reference procedure but can take weeks. Detection of circulating *H. capsulatum* antigen is very useful for diagnosis and follow-up of patients with disseminated histoplasmosis, but is unavailable in most countries in Europe, and serology is often negative in immunosuppressed patients. Recently, a reverse transcription-PCR technique has proved useful for fast, sensitive, and specific diagnosis; however, this technique is not available on a routine setting.

When a diagnosis of disseminated histoplasmosis is suspected, the GM assay, with its known cross-reactivity with *H. capsulatum* antigen, can be of interest. A previous study has shown that 69% of serum specimen that were positive for Histoplasma antigen were also positive in the GM assay, especially those with a high Histoplasma antigen level. The decrease of Histoplasma antigen serum titer is known to be well correlated in HIV-infected patients with response to treatment, and its increase with relapse. To our knowledge, the monitoring of the course of GM assay values in patients with disseminated histoplasmosis has not been described and could be helpful to assess response to therapy and to distinguish a relapse from an IRIS in HIV-infected patients. In our case, we indeed observed an early and significant decrease of GM index after antifungal therapy initiation, which was correlated with clinical improvement (Figure 1). When our patient was readmitted for a probable IRIS, the GM index had not risen, consistent with Histoplasma antigen titer (0.59 and 6.1 EIA, respectively, Figure 1). Thus, in areas such as Europe where it is available and inexpensive, GM assay can be a surrogate marker of disseminated histoplasmosis in patients with AIDS. However, in patients who do not have AIDS or with non-disseminated histoplasmosis, circulating antigen levels are lower and the GM assay may lack sensitivity.

On the other hand, BG exhibited a kinetic differing from other antigen-based markers: it was positive at diagnosis, significantly decreased after antifungal treatment initiation, but increased at the diagnosis of IRIS, which was made clinically and based on tissue reaction in addition to biological results (negative lymph node, blood, colon fungal cultures, and HIV viral load decreased by 2 log₁₀ copies/mL and CD4+ cells increased from 42/mm³ from total to 98/mm³ [from 2% to 10% of total lymphocytes], Figure 1). Preliminary data have reported BG detection in serum of patients with positive Histoplasma antigen. In a previous report, 87% of serum specimens positive for Histoplasma antigen
were found positive for BG.\textsuperscript{17} However, several authors have shown that BG was not reliable for monitoring the effectiveness of treatment in patients with \textit{Candida} endocarditis and in HIV-infected patients with \textit{Pneumocystis pneumonia}.\textsuperscript{18–20} Thus, if BG could also be a potential alternative to \textit{Histoplasma} antigen detection, this method would probably not be suitable for follow-up, is not yet commonly available, and is expensive.

In conclusion, positive \textit{Aspergillus} GM is a reliable surrogate marker of \textit{Histoplasma} antigen load in the follow-up of AIDS-associated disseminated histoplasmosis, especially when \textit{Histoplasma} antigen is not available in tropical areas and also in non-endemic areas such as Europe.

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