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Received: August 27, 2018. Accepted: April 2, 2019
Published online: April 26, 2019
DOI:10.7883/yoken.JJID.2018.354
Histoplasmosis among HIV-infected patients in Japan: A case report and literature review

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**Running title:** Histoplasmosis in HIV-infected patients in Japan

**Key words:** Histoplasmosis; *Histoplasma capsulatum*; HIV infection; non-endemic area; endemic mycosis
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Summary

Histoplasmosis is occasionally encountered in non-endemic countries owing to more frequent international travel and migration, as well as to an increase in the number of vulnerable hosts (e.g., patients with cellular immunodeficiencies). However, diagnosis of endemic mycoses may be challenging owing to its rarity and the limited availability of diagnostic tests. We report a case of disseminated histoplasmosis in a human immunodeficiency virus (HIV)-infected Japanese man who had often travelled to histoplasmosis-endemic countries. We also reviewed the reported cases of HIV-associated histoplasmosis in Japan. To the best of our knowledge, this is the ninth case report of co-infection with *Histoplasma* and HIV in Japan, and the second involving a Japanese patient. This case emphasizes the importance of noting the details of not only the present residence of patients but also their previous residence and travels. If histoplasmosis is suspected, physicians should inform laboratory personnel that fungal cultures should be incubated for 6 weeks, and compliance with biosafety guidelines for handling the specimens should be practiced. Since death occurred in nearly 50% of HIV-associated histoplasmosis in Japan, early recognition, timely diagnosis, and appropriate treatment are mandatory.
Histoplasmosis is an invasive infection caused by *Histoplasma capsulatum*, a thermally dimorphic fungus with two distinct varieties: *H. capsulatum* var. *capsulatum* (the most common variant worldwide) and *H. capsulatum* var. *duboisii* (the African variant). Histoplasmosis is endemic in certain regions of the United States (particularly in the Ohio and Mississippi river valleys), Mexico, Central and South America, Southeast Asia, India, China, Australia, parts of Europe (particularly Italy), and Africa (1). In Japan, histoplasmosis is considered to be a rare, imported mycosis, with only approximately 100 cases reported to date (2). Although fewer than 10 suspected autochthonous cases have been reported, *Histoplasma* spp. has never been recovered from environmental samples in Japan [for example, no *Histoplasma* strain was detected in 187 bat guano samples from 67 caves (3)].

Human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS) is a major risk factor for disseminated histoplasmosis. HIV infections/AIDS are much less prevalent in Japan than in Southeast Asian countries and in the United States, where histoplasmosis is endemic. Hence, patients co-infected with HIV and *Histoplasma* are rarely encountered in Japan. Moreover, there have been a few reports of histoplasmosis in HIV-infected Japanese patients.
Here, we report a case of disseminated histoplasmosis in an HIV-infected Japanese patient who had traveled extensively to endemic countries. We also present a literature review of HIV-associated histoplasmosis cases in Japan.

A previously healthy 40-year-old Japanese man presented to a community hospital in Tokyo with dry cough, fever, and progressively worsening dyspnea for 3 weeks. Chest computed tomography (CT) revealed bilateral ground glass opacities and a 17-mm nodule in the left lower lung lobe with mild mediastinal lymphadenopathy. He was diagnosed with AIDS-associated *Pneumocystis* pneumonia (PCP). The CD4$^+$ T lymphocyte count was 13 cells/µL, and plasma HIV RNA was 1,400,000 copies/mL. He was treated with sulfamethoxazole and trimethoprim, and then referred to our hospital for further management of his HIV infection and evaluation of the pulmonary nodule.

The patient worked as a consultant and had an extensive travel history. In the previous 22 years, he had visited over 30 countries in Asia, Europe, North America (including the west coast), South America, Africa, and the Middle East for business and personal purposes. His visits were mostly short-term, up to a few weeks, and in the past 3 years, mainly to Southeast Asian countries. Thailand (approximately 60 times), China (40 times), and Vietnam (approximately 30 times) were the three most-visited countries. The patient denied being in or near caves, chicken coops, or farms that were visibly
contaminated with bird or bat guano in these countries. He was sexually active with multiple male partners. His past medical history was unremarkable other than weight loss of 17 kg over a 2-year period.

His body temperature was 36.7°C; pulse rate, 100/min; blood pressure, 136/78 mm Hg; respiratory rate, 16/min; and oxygen saturation, 97% in ambient air. No thrush was noted, lung sounds were clear without crackles, and no rashes were observed. An ophthalmologic examination showed findings consistent with cytomegalovirus retinitis. An interferon-gamma release assay (T-SPOT.TB) was negative. A cytomegalovirus pp65 antigenemia assay was positive (293 cells per 100,000 white blood cells). The plasma β-D glucan level was elevated (802 pg/mL; reference, ≤20 pg/mL). Serum cryptococcal antigen was not detected.

A chest radiograph showed a 20-mm nodule in the left lower lung field, with little PCP-associated pulmonary infiltration. Antiretroviral (dolutegravir, abacavir, and lamivudine) and anti-cytomegalovirus (valganciclovir, 900 mg orally twice daily) therapies were initiated. One week after starting antiretroviral therapy, the patient developed a fever and rashes on his face, trunk, and extremities (Fig. 1A, B). Brown macules, small papules, and erythema were observed in these areas. He had no recurring respiratory symptoms. CT showed worsening lymphadenopathy in the mediastinal and
bilateral inguinal areas, and the pulmonary nodule, with slight increase in size, and improved ground grass opacities of both lungs (Fig. 1C, D). The plasma β-D glucan level was again elevated (3,450 pg/mL) despite successful treatment of the PCP. A test for the *Aspergillus* galactomannan antigen was positive (index value, 2.5; reference value, less than 0.5), although there was no evidence of aspergillosis.

Bronchoalveolar lavage fluid (BALF) specimen was obtained. Gram staining and bacterial culturing of the BALF showed no organisms. Neither *Mycobacterium tuberculosis* nor the *Mycobacterium avium* complex (MAC) was detected in polymerase chain reaction (PCR) assays. Before obtaining the culture results, fluconazole was empirically administered for invasive fungal diseases commonly observed in HIV-infected Japanese patients, such as cryptococcosis, and for primary prophylaxis against penicilliosis, given his extensive travel history to Southeast Asia (4). Although itraconazole was the first choice of primary prophylaxis of penicilliosis, fluconazole was used as an alternative due to limited availability of itraconazole at our institution, more drug interactions, high costs, and low tolerability of itraconazole. Three to four weeks later, an organism was observed in the fungal cultures of sputum and BALF (Fig. 2A, B) but not in cultures of blood. It was identified as *Histoplasma capsulatum* var. *capsulatum* by sequencing of the internal transcribed spacer region, D1/D2 26S rDNA,
and the *Histoplasma* M antigen. Disseminated histoplasmosis was diagnosed.

Intravenous liposomal amphotericin B (3 mg/kg daily) and oral itraconazole (200 mg twice daily) are the recommend agents for treating severe-to-moderate and less severe disseminated histoplasmosis, respectively (4). Because the patient’s symptoms had improved considerably at the time, fluconazole was switched to 400 mg itraconazole per day for histoplasmosis treatment.

He continued to undergo antiretroviral therapy, itraconazole, and prophylaxis for PCP and MAC disease. At the 6-month follow-up, CT showed that the lung nodule had decreased in size to 13 mm, and the mediastinal and inguinal lymphadenopathy and skin eruptions improved as well.

To date, only eight cases of AIDS-associated histoplasmosis have been reported in Japan (Table 1). The patients in these cases were aged 25–48 years and were mostly men. All had resided in histoplasmosis-endemic countries and are considered to be imported cases. Seven of the eight patients had emigrated from Africa, Southeast Asia, or Brazil. The only Japanese patient other than our patient was a 40-year-old bisexual man who developed AIDS-associated disseminated histoplasmosis in 1994; he had lived in the Midwest United States, the most histoplasmosis-endemic region in the country, from 1987 to 1990 (5). While our patient had no history of residence for a long period
of time in endemic regions, he had a history of extensive travels to endemic countries.

Seven patients presented with a disseminated form of histoplasmosis, while the eighth presented with cervical lymphadenitis. The median CD4+ T lymphocyte count was 5 cells/μL (range, 0.3–205 cells/μL). *H. capsulatum* var. *duboisii* was the causative agent in a Ugandan patient. In most patients, *Histoplasma* was present in cultures grown from blood, bone marrow, or other tissue samples, confirming the diagnosis. Four patients (44%) died from the disease.

In Japan, there are no commercially available tests for diagnosing histoplasmosis via antigen detection, antibody detection, or PCR. Diagnosis is also hampered by the slow growth of *Histoplasma* in culture (up to 6 weeks for colony formation) compared with that of other endemic fungi [e.g., 1–3 weeks (generally 5–10 days) for *Blastomyces* and within a week for *Coccidioides*] (6). Testing for the *Aspergillus* galactomannan antigen, which cross-reacts with the *Histoplasmosis* antigen, may be useful for diagnosing histoplasmosis when *Histoplasma* antigen testing is unavailable (7, 8); because invasive aspergillosis is relatively uncommon in AIDS patients, a positive result would raise suspicion of histoplasmosis. However, it is important to note that the galactomannan antigen may cross-react with the antigens involved in other endemic mycoses such as penicilliosis, paracoccidioidosis, and
blastomycosis (7, 9).

Finally, it needs to be emphasized that endemic mycosis including histoplasmosis, coccidioidomycosis, blastomycosis, and penicilliosis can be hazardous in microbiology laboratory given its highly infectious nature of conidia (17). It is recommended that cultures of these agents should be performed only at specialized laboratories (biosafety level 3). Therefore, when these infections are suspected, clinicians should alert the microbiology laboratory and contact a specialized laboratory and discuss the plan for processing and transporting potentially infectious specimens even before collecting them. In our case, the culture plate was completely sealed right after the BALF sample was inoculated. When growth was noted, the specimen was transported without opening the plate to the designated reference laboratory at National Institute of Infectious Diseases in compliance with the guidelines of the World Health Organization (18).
Acknowledgements

We thank Dr. Katsutoshi Abe at Kugayama Hospital for patient care.

Conflict of interest

None
References


Table 1. Reported cases of human immunodeficiency virus-associated histoplasmosis in Japan

<table>
<thead>
<tr>
<th>Case</th>
<th>Year reported</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Presumed country of acquisition</th>
<th>CD4+ (#/µL)</th>
<th>Diagnosis</th>
<th>Specimen source</th>
<th>Method of diagnosis</th>
<th>Variety</th>
<th>Outcome</th>
<th>Ref.</th>
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<tr>
<td>1</td>
<td>1999</td>
<td>40</td>
<td>Male</td>
<td>Japanese</td>
<td>United States (Midwest)</td>
<td>205</td>
<td>Disseminated infection</td>
<td>Blood</td>
<td>Culture</td>
<td>var. capsulatum (probable)</td>
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<td>2</td>
<td>2002</td>
<td>30</td>
<td>Male</td>
<td>Burmese</td>
<td>Myanmar</td>
<td>28</td>
<td>Lymphadenitis</td>
<td>Cervical lymph node</td>
<td>Culture</td>
<td>var. capsulatum</td>
<td>Survived</td>
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<td>3</td>
<td>2003</td>
<td>40</td>
<td>Female</td>
<td>Ugandan</td>
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<td>Bone marrow, CSF</td>
<td>Culture</td>
<td>var. dubosii</td>
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<td>2007</td>
<td>45</td>
<td>Male</td>
<td>Ghanaian</td>
<td>Ghana</td>
<td>20</td>
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<td>Blood, bone marrow, lung, liver, spleen</td>
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<td>40</td>
<td>Male</td>
<td>Ghanaian</td>
<td>Ghana</td>
<td>5</td>
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<td>2009</td>
<td>39</td>
<td>Male</td>
<td>Thai</td>
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<td>25</td>
<td>Female</td>
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<td>2013</td>
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<td>Brazil</td>
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<td>var. capsulatum</td>
<td>Survived</td>
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Abbreviations: Ref, reference; CSF, cerebrospinal fluid; BALF, bronchoalveolar lavage fluid
Figure legends

Fig. 1. Rashes on the chest (A) and upper back (B) that developed 1 week after the initiation of antiretroviral therapy. Chest computed tomography with contrast agents 1 week after starting antiretroviral therapy shows (C) a pulmonary nodule (arrowhead) and (D) markedly worse mediastinal lymphadenopathy (arrows).

Fig. 2. *Histoplasma capsulatum* isolated from bronchoalveolar lavage fluid (A) Sabouraud agar culture shows a white/buff-brown colony after 4 weeks of incubation at 30°C. (B) Macroconidia with digital projections in a representative colony as visualized microscopically (lactophenol cotton blue staining, × 400). Scale bar, 20 μm
Figure 1
Figure 2