Indigenous Case of Disseminated Histoplasmosis, Taiwan

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We report the first indigenous case of disseminated histoplasmosis in Taiwan diagnosed by histopathology of bone marrow, microbiologic morphology, and PCR assay of the isolated fungus. This case suggests that histoplasmosis should be 1 of the differential diagnoses of opportunistic infections in immunocompromised patients in Taiwan.

Histoplasma capsulatum, a dimorphic fungus that causes human disease, is endemic in North and Central America, particularly in the region of the Ohio and Mississippi River valleys. Humans are infected by inhalation of the mycelial fragments and microconidia of the organism. After the emergence of HIV infection, histoplasmosis has become 1 of many troublesome opportunistic infections among patients with AIDS. Patients receiving immunosuppressive agents are also predisposed to H. capsulatum infection (1). Although the organism is found worldwide, cases of histoplasmosis are rarely encountered in Taiwan; only a few, imported, cases have been reported in this decade (2–7). We report the first indigenous case of disseminated histoplasmosis in Taiwan.

The Case

In November 2005, a 78-year-old man with underlying rheumatoid arthritis was sent to the emergency department with generalized weakness and poor appetite of several weeks’ duration. He had received oral therapy with prednisolone (5 mg twice per day), hydroxychloroquine (200 mg twice per day), sulfasalazine (1,000 mg twice per day), and methotrexate (MTX) (15 mg per week) for 4 months. The patient’s body temperature was 38.5°C, blood pressure was 129/80 mm Hg, pulse rate was 76 beats/min, and respiratory rate was 20 breaths/min. Physical examination disclosed mild icteric sclera and multiple ecchymoses on the extremities.

A complete blood cell count showed a leukocyte count of 6,110/µL (4% bands, 77% segmented neutrophils, 7% lymphocytes, 6% normoblasts, and 3% myelocytes), hemoglobin level of 11.5 g/dL, and platelet count of 3,000/µL. Biochemical testing showed total bilirubin level of 3.89 mg/dL (normal 0–1.3 mg/dL) and alkaline phosphatase level of 480 U/L (60–220 U/L). Renal function, liver enzymes, and electrolyte levels were all within normal limits. The rheumatoid factor level was 76.3 IU/mL (normal <15 IU/mL). The erythrocyte sedimentation rate and C-reactive protein level were 30 mm/hour (0–20 mm/hour) and 100 mg/L (0–5 mg/L), respectively. Test results for HIV and antinuclear antibody were negative. A chest radiograph showed bilateral interstitial micronodules and a fibrocalkified pattern. Abdominal ultrasonography indicated splenomegaly. The patient was admitted with the tentative diagnosis of MTX-induced thrombocytopenia.

Bone marrow aspiration (Figure 1) and biopsy were performed because of refractory thrombocytopenia and the presence of young blood cells on the peripheral blood smears. Intravenous amphotericin B (0.7 mg/kg/day) was administered because disseminated histoplasmosis was highly suspected because of the bone marrow findings. Four weeks later, the fungal culture of the bone marrow showed growth of mold (Figure 2A and B). The microorganism was subsequently identified as H. capsulatum by PCR assay (Figure 2C) (8). No H. capsulatum was cultured from the patient’s peripheral blood or sputum.

The patient’s general condition improved after administration of a total dose of 1 g of intravenous amphotericin B, and the patient was discharged and treated with oral itraconazole, 200 mg once a day. Two weeks later, itraconazole therapy was suspended because impaired liver function was found. The patient was closely monitored for...

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Figure 1. A bone marrow biopsy specimen showing numerous oval-shaped intracellular and extracellular microorganisms (A and B). A bone marrow aspiration smear showed numerous intracellular yeastlike microorganisms (C and D). A) hematoxylin and eosin stain, ×1,000; B) periodic acid-Schiff stain, ×1,000; C) Gram stain, ×1,000; and D) Wright stain, ×1,000.
3 months, and no clinical evidence of histoplasmosis relapse was noted.

Conclusions

A variety of laboratory tests for diagnosis of histoplasmosis, including fungal culture, histopathology, serologic tests, antigen detection, and molecular methods, have different sensitivities based on clinical manifestations and host status (9). The standard for diagnosis is isolation of _H. capsulatum_ from culture. However, it usually requires ≈4 weeks to grow and has a low sensitivity rate (15%) in self-limited histoplasmosis. The knobby appearance of macroconidia and microconidia indicated by Lactophenol Cotton Blue Stain (Hardy Diagnostics, Santa Maria, CA, USA) of the mold form from fungal cultures is characteristic of _H. capsulatum_ (Figure 2B) (10). In histopathology, histoplasmosis is impressive, with its numerous ovoid-shaped microorganisms in infected tissue (Figure 1). However, without sufficient experience, one could misidentify _Blastomyces dermatitidis_, _Candida glabrata_, _Cryptococcus neoformans_, _Penicillium marneffei_, _Leishmania_ spp., _Pneumocystis jiroveci_, or _Toxoplasma gondii_ as _H. capsulatum_ (11). Despite a characteristic form, specific DNA probing is usually applied for faster definitive identification (12).

In areas where histoplasmosis is not endemic, including Taiwan, serologic tests, antigen detection reagents, and specific DNA probes for diagnosis of histoplasmosis are not universally available. Among serologic tests, immunodiffusion and complement fixation for anti- _Histoplasma_ antibody detection are widely applied; sensitivity rates are 95%–100% and 82%–90% for pulmonary and disseminated histoplasmosis, respectively. Some limitations occur, including the need for 2 to 6 weeks for antibody production after infection, impaired production of antibodies in immunosuppressed patients, and presence of cross-reaction mainly due to paracoccidioidomycosis, blastomycosis, and aspergillosis (9). Antigen detection in serum and urine is the most useful method of diagnosing histoplasmosis because it provides early diagnosis before culture and antibody production, monitors response of therapy, and detects relapse. The sensitivity rates of antigen detected are 25%–75% in pulmonary histoplasmosis and 82%–95% in disseminated histoplasmosis. Cross-reactions may occur in cases of paracoccidioidomycosis, blastomycosis, African histoplasmosis, and _P. marneffei_ (9).

Although the environment in Taiwan is suitable for _H. capsulatum_ to grow, histoplasmosis has been rarely encountered. In a survey of histoplasmin skin tests conducted in Taiwan in the 1950s, only 7 (0.19%) of 3,589 schoolchildren tested positive, and the author concluded histoplasmosis probably does not exist in Taiwan or is very rare (13). The first possible case of histoplasmosis in Taiwan was reported in 1977; however, the diagnosis was doubtful because it was based only on histopathologic findings in a cervical lymph node biopsy specimen, without definitive fungal culture or molecular identification (2). No further cases of histoplasmosis were reported in Taiwan until this decade, when 6 cases were reported (3–7). The clinical characteristics of these cases are summarized in the online Appendix Table (available from www.cdc.gov/ncidod/EID/13/1/127-appT.htm). All cases include a history of travel or residence outside Taiwan, where the patients might have acquired the infection; furthermore, most of the patients had underlying HIV infection. Diagnoses were mostly based only on histopathologic or morphologic findings in fungal cultures because the serologic tests, antigen detection reagents, and commercial DNA probes for diagnosis of histoplasmosis were not available in Taiwan. In contrast to these cases, our patient had never traveled outside Taiwan and did not have an HIV infection. To confirm the identification of _H. capsulatum_ on the basis of histopathologic and fungal form findings (Figures 1, 2A, and 2B), we applied a specific PCR assay as previously described (8), and the results were definitive (Figure 2C). The fibrocalcific nodules found on the chest radiograph imply that either 1) the patient might have had histoplasmosis for years and it became disseminated because of immunosuppressive...
therapy for rheumatoid arthritis or 2) the patient was rein-
fected with the calcified lesions that resulted from prior
histoplasmosis. The results indicate that this is the first
definitive indigenous case of disseminated histoplasmosis
in Taiwan. Nonetheless, we were unable to monitor our
patient’s response to treatment by antigen tests, as is recom-
mended (9,14), because they are not available in Taiwan.

The rarity of diagnosed histoplasmosis cases in
Taiwan could be explained in several ways. First, the diag-
nostic rate of histoplasmosis might be markedly decreased
because of the lack of serologic and antigen testing kits
and reagents, which are useful for diagnosis of self-limited
and nondisseminated histoplasmosis. Second, pulmonary
histoplasmosis might be misdiagnosed as tuberculosis,
which is prevalent in Taiwan. Third, physicians are unfa-
miliar with histoplasmosis and may consider that histo-
plasmosis is absent in Taiwan. With increasing
immunocompromised hosts resulting from immunosup-
pressive therapy and HIV infections, as well as improved
diagnostic tests, histoplasmosis might be an emergent
infectious disease in Taiwan in the future.

In summary, although an indigenous case of histoplas-
mosis had never been encountered, it should be 1 of the
differential diagnoses of opportunistic infections in
immunocompromised patients in Taiwan. The true preva-
lence of histoplasmosis in non-disease–endemic regions
might be underestimated because of the paucity of diag-
nostic tools and familiarity with histoplasmosis.

Dr Lai is an infectious disease specialist at E-Da Hospital in
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## Appendix Table. Clinical characteristics of cases of histoplasmosis reported in Taiwan*

| Ref | Age (y)/sex | Year of diagnosis | Manifestation | Signs and symptoms | Chest radiograph | Laboratory examination | Underlying disease | Diagnostic methods | Travel history | Treatment | Outcome |
|-----|-------------|-------------------|---------------|-------------------|------------------|-----------------------|-------------------|-------------------|---------------|-----------|---------|
| 2   | 32/M        | 1977              | Disseminated histoplasmosis | Cough, backache, neck LAP, anorexia, bodyweight loss | Enlarged hilar lymph nodes | Leukocytosis | None† | Lymph node biopsy only | None | Anti-TB drugs | Died    |
| 3   | 77/M        | 1994              | Laryngeal histoplasmosis | Sore throat, hoarseness | NA | Normal | Old pulmonary TB, adrenal insufficiency | Laryngeal biopsy and fungal culture | Europe, Indonesia, People’s Republic of China, Saudi Arabia, | Ketoconazole | Survived |
| 3   | 37/M        | 1996              | Disseminated histoplasmosis (skin, blood, bone marrow) | Fever and multiple papular skin rash | Normal | Pancytopenia | AIDS (CD4 count: NA), old pulmonary TB, cerebral toxoplasmosis | Skin, bone marrow, liver biopsy and fungal culture | Myanmar | Fluconazole | Died |
| 4   | 27/M        | 1997              | Gastrointestinal histoplasmosis | Fever, abdominal pain, watery diarrhea, bodyweight loss | Normal | Leukopenia, hypoalbuminemia | AIDS (CD4 count: 200/μL) | Colon tumor biopsy and fungal culture | Thailand, Malaysia, Singapore, Indonesia | AmB | Survived |
| 5   | 46/M        | 1999              | Disseminated histoplasmosis (skin, blood, pleural effusion) | Fever, skin ulcers, prolonged diarrhea, jaundice, hepatosplenomegaly | Bilateral pleural effusion | Leukocytosis, anemia, thrombocytopenia, hypercalcemia | Nontyphoid salmonellosis | Skin biopsy and skin, blood, and pleural fungal culture; AccuProbe for pathogen identification | Indonesia | AmB | Died |
| 6   | 30/M        | 2000              | Disseminated histoplasmosis | Abdominal pain, generalized LAP, hepatosplenomegaly | Normal | Anemia, thrombocytopenia | AIDS (CD4 count: 76/μL) | Stomach and lymph node biopsy | Unknown, but he was a sailor | AmB | Died |
| 7   | 55/M        | 2004              | CNS histoplasmosis and disseminated TB | Fever, bodyweight loss, and poor appetite, hepatosplenomegaly | Bilateral numerous nodules | Pancytopenia | AIDS (CD4 count: 2/μL) | CSF fungal culture | Myanmar, People’s Republic of China | AmB | Died |
| PR  | 78/M        | 2006              | Disseminated histoplasmosis | Fever, general weakness, anorexia, splenomegaly | Interstitial micronodules | Anemia, thrombocytopenia | Rheumatoid arthritis treated with methotrexate and prednisolone | Bone marrow aspiration biopsy and culture; PCR assay for pathogen identification | None | AmB | Survived |

*Ref, reference; LAP, lymphadenopathy; TB, tuberculosis; NA, data not available; AmB, amphotericin B; CNS, central nervous system; CSF, cerebrospinal fluid; PR, present report.
†HIV examination was not available in Taiwan until the 1980s.

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