J Infect Chemother (2007) 13:51–55
DOI 10.1007/s10156-006-0486-3

CASE REPORT

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HIV infection with concomitant cerebral toxoplasmosis and disseminated histoplasmosis in a 45-year-old man

Received: August 28, 2006 / Accepted: October 13, 2006

Abstract Although disseminated histoplasmosis is a common opportunistic infection in HIV patients in endemic areas, it is not widely known in Japan. We report a rare case of a man from Ghana infected with HIV who was hospitalized in Japan and who suffered from coinfection with cerebral toxoplasmosis and disseminated histoplasmosis. The diagnosis of cerebral toxoplasmosis was confirmed by a brain biopsy, and the therapy for the disease resulted in almost complete resolution of the brain lesion. However, fever of unknown origin continued for 2 weeks, and disseminated histoplasmosis was diagnosed by examination of a blood smear and by the detection of the histoplasma genome in the peripheral blood by means of polymerase chain reaction. The isolate was confirmed to be *Histoplasma capsulatum* var. *duboisii*. Therapy with amphotericin B was initiated, and no histoplasma genome in the peripheral blood was detected 3 days later. Unfortunately, the patient died after 10 days from acute respiratory syndrome. This case highlights that histoplasmosis should be included in the differential diagnosis of opportunistic infections in AIDS patients when patients have a history of travel to or arrival from endemic areas.

Key words Human Immunodeficiency Virus (HIV) · Toxoplasmosis · Histoplasmosis · Imported mycosis

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Introduction

The introduction of highly active antiretroviral therapy (HAART) has decreased the incidence of acquired immunodeficiency syndrome (AIDS)-defining diseases.[1] However, opportunistic infections are still a major cause of death in human immunodeficiency virus (HIV)-infected patients in the HAART era, especially in long-term infected patients who do not receive prophylaxis.[2] *Toxoplasma gondii* infection occurs worldwide, and AIDS-related cerebral toxoplasmosis is a life-threatening infection of the central nervous systems (CNS).[3] *Histoplasma capsulatum* infection is a common endemic mycosis in the United States and Africa. Although histoplasmosis is mostly self-limiting, the disease causes the progressive disseminated form in severely immunocompromised hosts such as AIDS patients.[4] It is difficult to diagnose the disease in nonendemic areas because of the nonspecific clinical symptoms, such as fever and weight loss. Here we report the rare case of an HIV-infected Ghanaian patient, who was living in Japan, with concomitant cerebral toxoplasmosis and disseminated histoplasmosis.

Case report

A 45-year-old Ghanaian man, who had migrated from Ghana and lived in several countries in Europe, including the Netherlands, Germany, and Britain, came to Japan in 1995 after marrying a Japanese woman. Diagnosed with HIV infection at our outpatient clinic on July 12, 1995, his $CD4^+$ T-cell count was 400/μl and he had no AIDS-defining diseases. He stopped attending the clinic after June 1996, but in May 2001, he attended the clinic, suffering from weight loss of 10 kg and herpes-zoster, and presented with a headache, left facial nerve palsy, and an atactic gait. On August 13, 2001, he was hospitalized in a neurosurgery hospital for treatment of a brain mass extending from the right basal ganglia to the midbrain, confirmed by computed tomography (CT), and a brain biopsy was performed be-

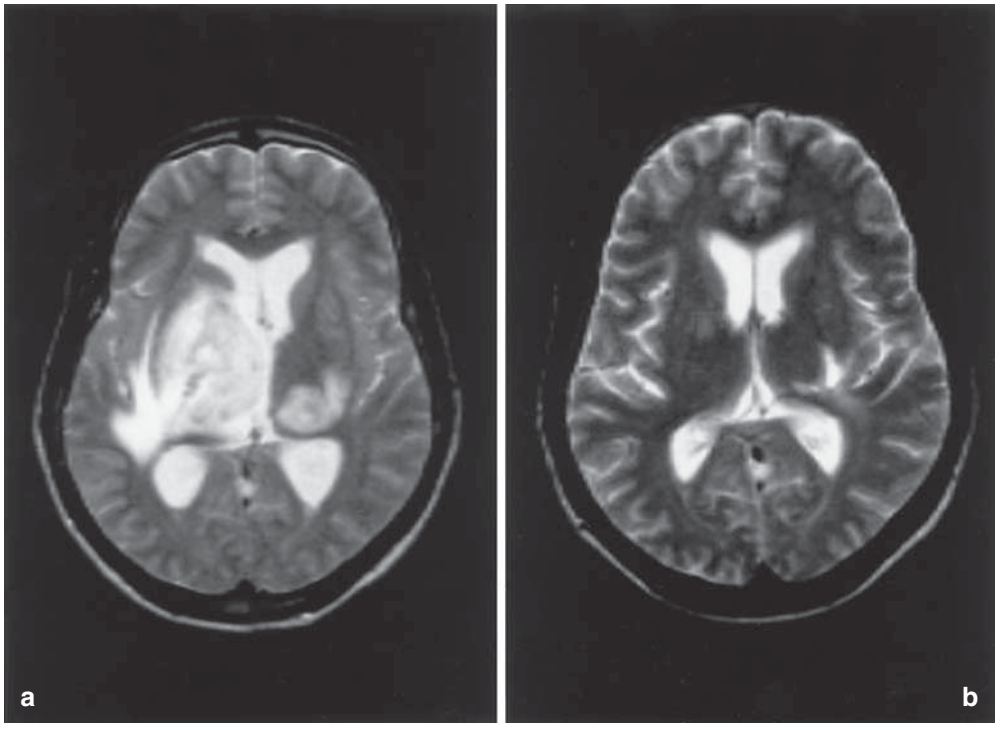


Fig. 1. **a** On admission, T2-weighted magnetic resonance (MR) image with contrast medium showed an enhancing mass extending from the right basal ganglia to the midbrain. **b** The mass had disappeared after 8 weeks of therapy for toxoplasmosis

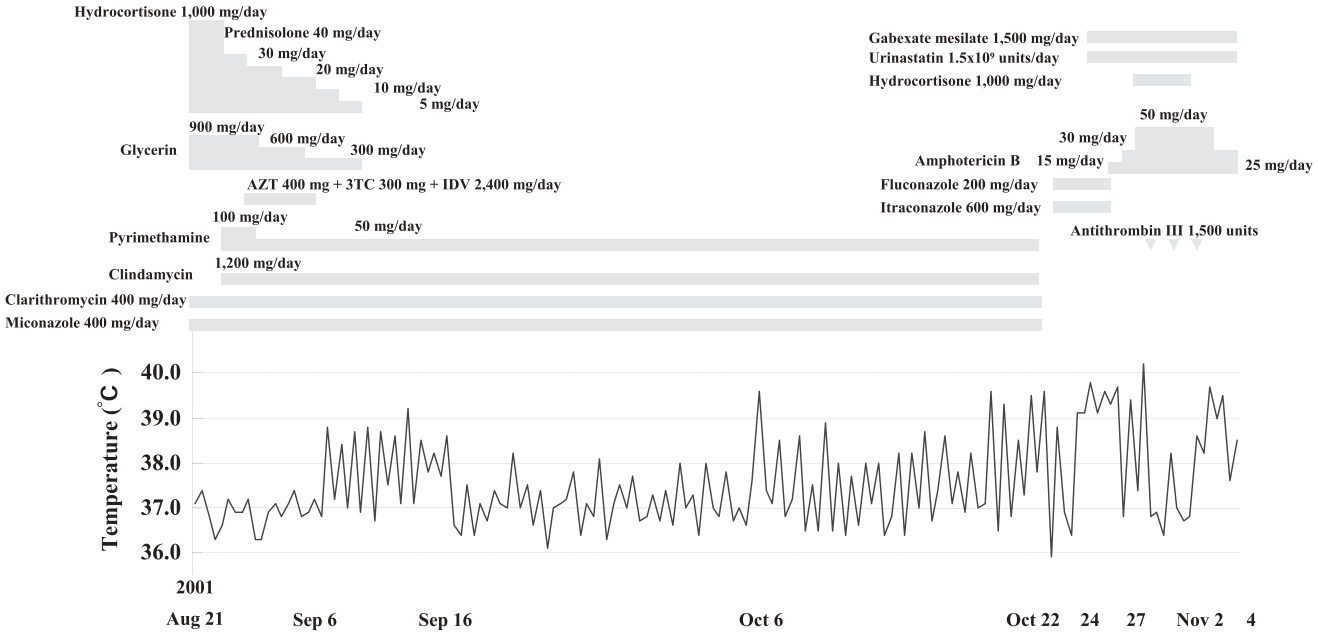
cause of a suspicion of CNS lymphoma. After therapy with steroids and glycerin was started for cerebral edema, he was sent to our hospital on August 21.

On admission, his consciousness level was Glasgow Coma Scale 15, his height was 163 cm; body weight, 56.4 kg; body temperature, 36.5°C; blood pressure, 144/80 mmHg; and pulse rate, 92/min and regular. There was no anemia or jaundice. The pupils were isochoric and round, light reflex was prompt, and ocular movement was intact, but right ptosis and left facial palsy were noted. The cervical lymph nodes were not palpable, but oral candidiasis was found. Heart and respiratory sounds were normal, and abdominal examination revealed mild splenomegaly. Pretibial edema was absent. Neurological examination revealed left hemiplegia and pyramidal tract signs.

The white blood cell count was 7360/μl (neutrophils 71%, lymphocytes 16.5%, monocytes 11.5%), red blood cells were 459×10^4/μl, hemoglobin was 13.5 g/dl, the platelet count was 27.2×10^4/μl, and the serum levels of lactate dehydrogenase and C-reactive protein were 370 IU/l and less than 0.06 mg/dl, respectively. The plasma HIV-RNA level and $CD4^+$ T-cell count were $10^{5.6}$ copies/ml and 24/μl, respectively. Magnetic resonance imaging (MRI) of the head revealed a contrast-enhancing mass lesion with peripheral edema extending from the right basal ganglia to the midbrain, as shown in Fig. 1a.

The clinical course of the patient is shown in Fig. 2. Pyrimethamine at 50 mg/day and clindamycin at 1200 mg/day were administered from August 25, 2001, because, from the tentative report of the brain biopsy, his condition was highly suggestive of cerebral toxoplasmosis rather than CNS lymphoma. HAART, including zidovudine, lamivudine, and indinavir, was initiated on August 27. Afterwards, the patient was diagnosed with cerebral toxoplasmosis, because serum anti-*Toxoplasma* IgG was positive (188.83 IU/ml) and brain biopsy revealed parasites in the oocysts, by positive staining for *T. gondii*-specific immunoperoxidase. The patient responded to the therapy for toxoplasmosis within 2 weeks, and the mass had disappeared on MRI after 8 weeks of the therapy, as shown in Fig. 1b. Although he suffered from fever and pancytopenia at the beginning of September, the symptoms were alleviated after the discontinuation of HAART. However, the patient again presented with high fever, that lasted for 2 weeks from the middle of October, and he developed pneumonia and acute renal failure on October 24. Staining of a blood smear on October 24 (Fig. 3a) revealed the phagocytosis of yeast-like microorganisms by granulocytes, and the histoplasma genome was detected in the peripheral blood by polymerase chain reaction (PCR) on October 25, on analysis at Teikyo University Institute of Medical Mycology. The isolate was confirmed to be *Histoplasma capsulatum* var. *duboisii* by the nucleotide sequences of the internal transcribed spacer (ITS) region (ITS1-5.8S rDNA-ITS 2).[5] The patient was diagnosed with disseminated histoplasmosis and was started on intravenous amphotericin B deoxycholate at 0.7 mg/kg per day. Although no histoplasma genome was detectable in the peripheral blood 3 days later, the patient developed acute respiratory distress syndrome (ARDS), and died on November 5, 2001.

On autopsy, histoplasmosis, by histological examination, was found to have disseminated into the bilateral lungs, liver, spleen, and bone marrow, where numerous small (2–5 mm in diameter) yeast-like microorganisms were found by Grocott's staining. *H. capsulatum* isolated from blood on October 26 was cultured for 4 weeks on brain heart infusion



WBC (/μL)	7,360	3,240	5,210	2,650	3,080	2,340	1,760	7,040	21,340	25,340
Hb (g/dL)	13.5	11.2	9.8	10.5	9.7	9.4	6.5	6.7	7.6	5.9
PLT (x10⁴/μL)	27.2	2.6	22.1	29.2	12.5	8.8	8.8	8.2	3.1	2.3
CRP (mg/dL)	0.06	3.52	12.81	1.89	5.61	12.64	25	> 40	9	37.8
LDH (IU/L)	370	212			576	1,482	4,185	3,200	1,915	2,335
Cr (mg/dL)	0.6	0.75		1.13	1.7	1.8	7.1	8.0	1.8	7.4
CD4 (/μL)	24									
HIV-RNA (copies/mL)	$10^{5.6}$									
Histoplasma genome in the peripheral blood							(+)	(+)	(-)	(-)

Fig. 2. Clinical course. *AZT*, zidovudine; *3TC*, lamivudine; *IDV*, indinavir; *WBC*, white blood cell count; *Hb*, hemoglobin; *PLT*, platelet count; *CRP*, C-reactive protein; *LDH*, lactate dehydrogenase; *Cr*, creatinine

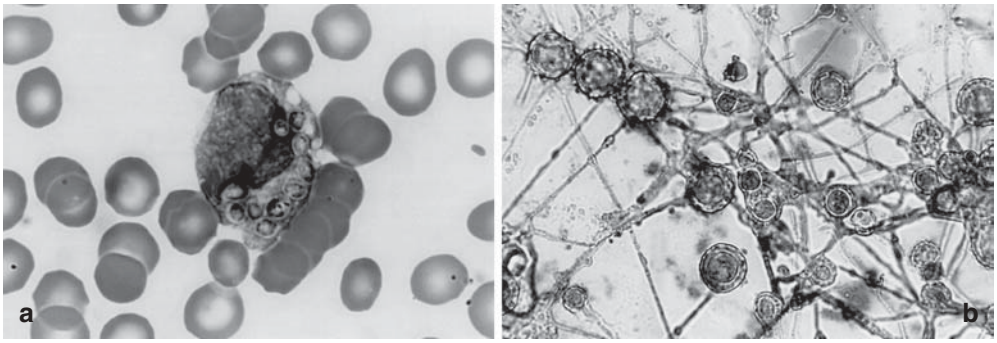


Fig. 3. **a** On October 24, peripheral blood smear showed circular inclusions in the cytoplasm of granulocytes. **b** A blood culture on brain heart infusion agar, at 25°C, after 4 weeks showed mold growth in the mycelial form, with hyphae-bearing conidia. **a** Wright-Giemsa, ×1000; **b** lactophenol cotton blue, ×400

agar at 25°C (Fig. 3b). Malignant lymphoma and Kaposi's sarcoma were not found. Acute renal failure was caused by disseminated intravascular coagulation (DIC). The cause of death on autopsy was ARDS.

Discussion

Few cases of concomitant parasite and fungus infection with toxoplasmosis and histoplasmosis have been reported in AIDS patients living in Japan.

Cerebral toxoplasmosis is one of the most common opportunistic neurological infections in AIDS patients, and typically occurs in patients with advanced AIDS.[3] Toxoplasmosis is caused by the protozoan parasite *T. gondii*. Infection in humans results from ingesting tissue cysts contained in undercooked or uncooked meat, or from ingesting food and water contaminated with oocysts from infected cat feces. In immunodeficient patients, toxoplasmosis is thought to be the result of the recrudescence of a latent infection acquired in the distant past.[6,7] The incidence of toxoplasmosis in patients with HIV has decreased since the

introduction of HAART and the broad use of trimethoprim-sulfamethoxazole (TMP-SMX) for *Pneumocystis carinii* pneumonia prophylaxis, but the disease can develop in AIDS patients undiagnosed for HIV infection or not receiving the antiretroviral therapy or the antitoxoplasmal prophylaxis, as occurred in our patient.[2,3,8] Diagnosis of cerebral toxoplasmosis in HIV-infected patients is based on progressive neurological deficits, serology such as the use of anti-*T. gondii* IgG titers, contrast-enhancing mass lesions on CT or MRI, or successful response, within 2 weeks, to specific treatment.[9] A brain biopsy should be performed in patients with a single lesion on MRI, a negative IgG test, an inadequate clinical response, or progression despite optimal therapy. Our patient was diagnosed with cerebral toxoplasmosis by a positive serum anti-*Toxoplasma* IgG test and a brain biopsy that was done in a neurosurgery hospital. Primary therapy for the disease is a pyrimethamine 200-mg load, then 50 mg/day, with sulfadiazine at 1 g, four times daily (or with clindamycin 600 mg four times daily) with folinic acid 10 mg/day.[6]

It remained unclear why our patient suffered from fever and pancytopenia at the beginning of September after therapy with pyrimethamine for cerebral toxoplasmosis and after HAART for HIV was started. A possible explanation is that the pancytopenia might have been induced by the pyrimethamine or zidovudine, or the fever might have been caused by immune reconstitution inflammatory syndrome (IRS) for the toxoplasmosis. IRS in patients with HIV is an adverse consequence of the restoration of a pathogen-specific immune response during the initial months of HAART, and cases in which IRS, caused by cerebral toxoplasmosis, occurred after the early initiation of HAART have been reported.[10–12]

H. capsulatum is a dimorphic fungus, and two varieties of the fungus are pathogenic in humans: *H. capsulatum* var. *capsulatum*, which is endemic in Central and South America, causes histoplasmosis capsulati; and *H. capsulatum* var. *duboisii*, which is endemic in Central and West Africa, causes histoplasmosis duboisii.[13] The infection is transmitted by conidia inhalation, and disseminated histoplasmosis is often seen in AIDS patients living in endemic areas; it is included among AIDS-defining infections. Histoplasmosis is a rare disease in Japan, and is considered as an imported mycosis. Because the majority of patients with histoplasmosis occurring in Japan are infected by *H. capsulatum* var. *capsulatum*,[14] our case, which was confirmed to be an infection by *H. capsulatum* var. *duboisii*, is valuable. In our patient, it was thought that a latent infection had been reactivated with impaired cellular immunity many years after his exposure to the infective agent in Africa; such reactivation of a latent infection is similar to that of tuberculosis. The clinical symptoms of the disease, such as fever, malaise, and weight loss are nonspecific, and these symptoms are found in 90% of those with AIDS. Physical examinations revealing hepatosplenomegaly and cervical lymphadenopathy, and laboratory findings revealing hematologic disturbance and anemia, as well as leukopenia and thrombocytopenia, are frequently observed. The diagnosis of histoplasmosis can be done by culturing blood, respiratory tract secretions, bone marrow, or focal infections.[13] However, culture is not useful when a rapid diagnosis is necessary, because the growth of *H. capsulatum* is slow and culture takes up to 6 weeks. Histoplasma antigen detection, by enzyme-linked immunosorbent assay (ELISA) of serum or urine, has become available for the rapid diagnosis of disseminated histoplasmosis in the United States, but this test is not available in Japan.[13] In our patient, a peripheral blood smear and antigen detection by PCR led to a rapid diagnosis. PCR appears to be useful for the diagnosis of disseminated histoplasmosis, although it is still not in wide clinical use for this purpose. Disseminated histoplasmosis is catastrophic if untreated. Intravenous amphotericin B is widely accepted as the initial therapy for the moderate and severe forms of disseminated diseases.[15] In our patient, no *H. capsulatum* was detected by PCR in the peripheral blood 3 days after the introduction of amphotericin B, indicating that the therapy was effective. However, some patients develop sepsis-like syndromes such as ARDS and DIC despite therapy, as did our patient.

Although early diagnosis is important for recovery from disseminated histoplasmosis, the diagnosis of the disease in Japan may be delayed because Japan is not an endemic area and the symptoms of this disease are nonspecific. However, the number of patients with imported mycoses such as histoplasmosis has recently increased in Japan,[14] and therefore imported mycoses should be included in the differential diagnosis of opportunistic infections in AIDS-patients when the patients have a history of travel to or arrival from an endemic area.

Acknowledgments The authors thank Dr. Koichi Makimura, from the Teikyo University Institute of Medical Mycology, Tokyo, Japan, for the sequential analysis of *H. capsulatum*.

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