

CASE REPORT

THE FIRST REPORTED CASES OF DISSEMINATED HISTOPLASMOSIS IN CAMBODIA, COMPLICATED BY MULTIPLE OPPORTUNISTIC INFECTIONS

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Abstract. Although disseminated histoplasmosis is recognized as a common opportunistic infection in HIV-infected persons living in endemic areas, it is not widely reported in Southeast Asia, and has not been reported in Cambodia. It remains unanswered whether this is secondary to a low disease prevalence, or whether the disease, which is associated with a nonspecific clinical presentation, is under diagnosed. In addition to a review of the literature regarding histoplasmosis in Southeast Asia, we provide a description of two HIV-1 infected patients with documented disseminated histoplasmosis complicating other opportunistic infections in Phnom Penh, Cambodia. These two cases highlight the need for both a high clinical suspicion, and reliable laboratory testing, in a setting where there is likely to be more than one infection complicating the patient's clinical course.

INTRODUCTION

Cambodia is a largely rural country. During the civil war of the late 1970's, all Cambodian citizens were forced to work in rural and agricultural settings. If *Histoplasma capsulatum* is present in Cambodian soil, exposure and latent infection are likely to be extremely common. Given the high rates of HIV-1 infection in Cambodia, histoplasmosis should be expected to be a common opportunistic infection. A review of the literature, however, revealed no reported cases of disseminated histoplasmosis in Cambodia. We describe two HIV- infected patients with disseminated histoplasmosis complicating other infections. These patients were participants in a prospective survey of newly diagnosed HIV-1 infected patients, which provided comprehensive laboratory assessments otherwise not avail-

able on a routine basis. In addition to their importance as the first reported cases of histoplasmosis in Cambodia, these cases highlight that empiric treatment of a single opportunistic infection in profoundly suppressed, HIV-1 infected, patients may easily miss other serious co-infections.

CASE 1

A 20 year old female presented with ten days of fever, chills, weight loss, nausea, vomiting and severe abdominal pain. Her history was significant for recent herpes zoster and a sexual assault in 1994. Vital signs showed a blood pressure of 90/50 mmHg, a pulse of 120 beats per minute, and a respiratory rate of 34 breaths per minute. On physical examination, she had extensive oral thrush, bilateral cervical adenopathy, a distended abdomen that was tender in the right upper quadrant, and a liver palpable five centimeters below the costal margin. Laboratory studies showed anemia and thrombocytopenia, a CD4 count of 4 cells/mm³, and a negative

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malaria smear. Blood cultures were obtained and two paired rapid HIV tests were positive. A chest radiograph was unremarkable. Abdominal ultrasound confirmed hepatomegaly without abscess. The patient was treated with metronidazole, ofloxacin, and nystatin, and asked to follow-up at one week.

One week later, her symptoms persisted and she was admitted to the hospital. Although her right upper quadrant pain became less severe, she continued to have high fevers and vomiting. Repeat chest radiograph and lumbar puncture done 15 days after presentation were unremarkable. Repeat abdominal ultrasound showed an increase in the liver span. Clinically, the patient worsened with hypotension (70/50 mmHg), tachycardia (120 beats per minute), and fever (T 40°C). On day 16, her initial blood culture grew *H. capsulatum*. She was resuscitated with normal saline and given amphotericin B. She completed a 14-day course of amphotericin B, followed by fluconazole for suppression. She returned to her job as a factory worker approximately one month after her initial presentation.

CASE 2

A 23 year old man presented to the hospital complaining of three days of sharp right lower quadrant pain, a 20 kg weight loss over two months, high fever, and a productive cough. On physical examination his blood pressure was 80/50 mmHg, pulse 140 beats per minute, respirations 32 breaths per minute, temperature 37.7°C, and oxygen saturation 88% on room air. He had extensive oral thrush and hairy leukoplakia. He had rebound tenderness over the right lower quadrant of the abdomen without a palpable mass. Ultrasound of the abdomen showed nephrolithiasis. Chest radiograph had a diffuse interstitial pattern. Paired rapid HIV tests were positive. Tuberculosis sputum specimens and malaria smears were negative. He had anemia and thrombocytopenia by complete blood count. His urine had 50 red blood cells per high power field. CD 4 cell count was 4 cells/mm³.

He was admitted to the medical ward with surgical consultation. He was treated for a presumed intra-abdominal infection and *Pneumo-*

cystis carinii pneumonia (PCP). His symptoms persisted, and on the 7th hospital day his admission blood culture grew *Cryptococcus neoformans*. He was given amphotericin B and after 3 days he began to improve clinically. After 4 weeks his admission blood culture also grew *H. capsulatum*. He was discharged on fluconazole for secondary prophylaxis.

DISCUSSION

Disseminated histoplasmosis is recognized as a common opportunistic infection in HIV-infected persons living in endemic areas. Most cases in the published literature are from the Americas, where HIV-1 prevalence is relatively low. A worldwide survey of histoplasmin skin sensitivity found the highest reactor rates in the United States, Central, and South America (Edwards and Billings, 1971). In parts of Southeast Asia, reactor rates were found to be 30 %. Despite this, disseminated histoplasmosis in Southeast Asia has rarely been reported in the literature, and prior to this there had been no published reports of histoplasmosis in Cambodia, where the HIV-1 epidemic is widespread (Randhawa *et al*, 1970; Symmers, 1972; Navarro *et al*, 1992; Wang *et al*, 1996). Published cases in Singapore (Wang *et al*, 1996) and Malaysia (Ng and Siar, 1996) suggest that histoplasmosis may be more prevalent in the region than is suggested by the literature. Although histoplasmin reactor rates are relatively high in the region, there is wide variability in these reactor rates across Thailand (Taylor *et al*, 1968). *H. capsulatum* can have substantial variations in prevalence in the environment, and in human infection, based on environmental conditions and human activities that bring susceptible hosts into contact with the organism. This is a particularly important issue in Cambodia, which has the highest HIV-1 prevalence in Asia, and will likely experience a high burden of these opportunistic infections.

Previous studies have shown a high prevalence of multiple opportunistic infections among patients with newly diagnosed HIV infection in Phnom Penh (Senya *et al*, 2003). These cases demonstrate the necessity to maintain vigilance

in this setting, not only for alternative diagnoses, but also for multiple concomitant illnesses. With antiretroviral therapy in short supply in Cambodia, clinical skills in the management of opportunistic infections is critical in this setting.

These cases also highlight the difficulty in diagnosing disseminated histoplasmosis in an environment where resources are limited, and fever, weight loss, abdominal pain, and atypical chest radiography are the nonspecific symptoms of many common infectious diseases. Although the outcomes for these patients were satisfactory, their hospital stays were prolonged by delays in diagnosis. More studies are needed to assess the actual prevalence of disseminated histoplasmosis in HIV-infected patients in Southeast Asia, as this will raise clinical suspicion, improve diagnosis and treatment, and determine the potential need for, and utility of, primary prophylaxis.

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