

# CASE STUDIES in the ANTIFUNGAL TREATMENT of HIGH-RISK PATIENTS

## Cryptococcus Infection in a CLL Patient

### CASE PRESENTATION:

#### *Cryptococcus* Infection in a CLL Patient

This was a 70-year-old man with heavily pretreated (FCRX3, alemtuzumab, CHOP-R, COP-R) active chronic lymphocytic leukemia (CLL). The patient had a history of *Escherichia coli* septicemia with pyomyositis in both lower extremities, and he had been on aztreonam (2 g q8h) and intravenous (IV) amikacin (10 mg/kg/day) for 6 weeks. He developed postchemotherapy pancytopenia (white blood cell count,  $0.3 \times 10^3/\mu\text{L}$ ) and a temperature of  $38.3^\circ\text{C}$ . The patient was not on antifungal prophylaxis. He was clinically stable without respiratory, urinary, gastrointestinal, or central nervous system (CNS) symptoms. On physical examination, he had no crackles or friction rub on auscultation of his chest, his abdomen was benign, and his catheter site was without exit-site tenderness or erythema. He had no sinus tenderness, periodontitis, onychomycosis, perirectal tenderness, rash, or disseminated skin lesions; his myositis was resolving. His blood urea nitrogen, creatinine, and liver function tests were within normal

limits, and his chest x-ray was clear. Serum *Aspergillus* galactomannan (enzyme-linked immunosorbent assay) and cytomegalovirus antigens were negative. On the same day, 2 sets of blood cultures (taken from the previous week) from a peripheral site grew 2 to 5 CFU/mL of yeasts. Therapy is initiated (by the hematology team) on IV caspofungin 70 mg on day 1 and 50 mg/day thereafter, pending the identification of yeasts, and an infectious diseases consult is called. The clinical laboratory is called, and the preliminary impression of yeasts in blood cultures is *Cryptococcus neoformans*. A serum cryptococcal antigen is obtained and is positive at a titer of 1:64. Urine cultures are negative for *Cryptococcus*. Caspofungin is discontinued, and therapy is initiated with a lipid-based amphotericin B agent 5 mg/kg/day plus fluconazole 400 mg/day. In the following days, the patient remains clinically stable with no evidence of CNS, pulmonary, or cutaneous involvement.

In this issue, Dimitrios P. Kontoyiannis, MD, presents a case report of cryptococcosis in a patient with advanced chronic lymphocytic leukemia (CLL). Up to 50% of patients with CLL may suffer from recurrent infections. A wide array of infections in CLL are typically seen in those with advanced disease and exposed to multiple chemotherapeutic regimens. Risk factors for infections are multiple, namely cellular immune dysfunction, granulocytopenia (induced by leukemic marrow/drug toxicity), hypogammaglobulinemia, complement deficiency, and asplenia. Pathogens include bacteria (eg, *Pneumococcus*, *Listeria*), mycobacteria, viruses (eg, herpes family), and fungi (eg, *Pneumocystis*). Opportunistic infections are usually seen with the use of drug regimens containing nucleoside analogues (eg, fludarabine) and alemtuzumab, particularly in combination with corticosteroids and other cytotoxic agents.

Management of cryptococcosis in patients not infected with the human immunodeficiency virus is poorly defined. The case report illustrates that not all yeasts in blood are *Candida*. The yeast turned out to be *Cryptococcus*, contrary to what the clinicians thought; hence, caspofungin was an inappropriate choice. With traditional polyene-based therapy, the patient's condition improved; however, given the underlying profound immunocompromise, the patient may have developed a second infection with *Aspergillus*. Continued vigilance and timely therapeutic changes led to successful management of this patient's opportunistic infection(s).

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## Educational Objectives

- Determine how therapeutic choices for invasive fungal infections can be most appropriately employed in high-risk patients
- Explore methods to improve patient outcomes, considering antifungal efficacy, spectrum of activity, safety, and cost-effectiveness
- Compare and understand the clinical uses of available antifungal agents

## CME Information

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## Question & Answer

### When should cryptococcosis be suspected?

*Cryptococcus neoformans* is an encapsulated, round or oval yeast that is globally distributed. It is presumed that infection with this fungus occurs because of inhalation of airborne cryptococci from environmental sources.<sup>1</sup> Although infection can occur in healthy individuals, the majority of patients who develop *Cryptococcus* infection are immunocompromised. Indeed, cryptococcosis is a well-recognized fungal infection occurring in patients with acquired immune deficiency disease (AIDS), but it also occurs in patients with cancer and other disorders associated with cell-mediated immunity, although at a much lower rate. Corticosteroid use is also associated with an increased risk for the disease.<sup>2</sup>

Among the cancer population, patients with leukemia and lymphoma are particularly susceptible to infection with *C neoformans*. In a study cohort of 31 cancer patients with culture-proven cryptococcosis, 20 (65%) had a hematologic malignancy, especially lymphoid malignancy.<sup>3</sup> Most patients (19 cases) presented with pulmonary cryptococcosis;

however, there were 6 cases of disseminated disease, 3 cases of meningitis, and 3 cases of other less common clinical forms of cryptococcosis. Of the 19 cases of pulmonary cryptococcosis, 6 (32%) were asymptomatic. For the other 13 (68%) patients, symptoms included fever and respiratory abnormalities, such as dyspnea, cough, pleuritic chest pain, and acute respiratory failure.

In our patient, blood cultures revealed a yeast infection, and therapy with caspofungin was initiated. Although a yeast infection with *Candida* spp is common in patients with hematologic malignancy, infection with other non-*Candida* opportunistic yeasts, such as *Cryptococcus* or *Trichosporon*, cannot be ruled out, especially in high-risk patients. Caspofungin, like other echinocandins, has activity against *Candida* spp but is not active against *Cryptococcus* and *Trichosporon*. Consequently, when we learned that the infection was due to *Cryptococcus*, caspofungin therapy was discontinued.

### Table.

#### Preferred Treatment Options for Cryptococcal Disease in Patients Not Infected With HIV<sup>4</sup>

Cryptococcal disease, treatment regimen
<b>Pulmonary</b> Mild to moderate symptoms or culture-positive specimen from this site Fluconazole, 200-400 mg/day for 6-12 months Itraconazole, 200-400 mg/day for 6-12 months Amphotericin B, 0.5-1 mg/kg/day (total, 1000-2000 mg) Severe symptoms and immunocompromised hosts Treat like CNS disease
<b>CNS</b> Induction/consolidation: amphotericin B, 0.7-1 mg/kg/day plus flucytosine, 100 mg/kg/day for 2 weeks, then fluconazole, 400 mg/day for minimum 10 weeks Amphotericin B, 0.7-1 mg/kg/day plus flucytosine, 100 mg/kg/day for 6-10 weeks Amphotericin B, 0.7-1 mg/kg/day for 6-10 weeks Lipid formulation of amphotericin B, 3-6 mg/kg/day for 6-10 weeks

HIV, human immunodeficiency virus; CNS, central nervous system.  
(Adapted from Saag MS et al. *Clin Infect Dis*. 2000; 30:710-718 with permission).

## Which antifungal agents have activity against *Cryptococcus*?

When it was determined that the yeast in blood cultures was *C neoformans*, we discontinued caspofungin and started combination antifungal therapy with a lipid-based amphotericin B agent and fluconazole. As mentioned already, the echinocandin class of agents does not have activity against *Cryptococcus*. Lipid-based amphotericin B products are usually preferred over the conventional deoxycholate formulation because of less nephrotoxicity and infusion-related toxicities. Notably, many of the current recommendations for treatment of cryptococcosis in patients not infected with the human immunodeficiency virus (HIV) are derived from experience in HIV-infected patients (Table).<sup>4</sup> Combination therapy with amphotericin B and flucytosine is standard therapy in immunocompromised hosts with pulmonary cryptococcal disease; however, at our institution, we rarely use flucytosine in our leukemic population because of the risk for myelosuppression with this agent. Also, with pulmonary cryptococcosis in patients without HIV infection, it is important to know that the optimal therapy and duration of therapy are as yet undefined.

As monotherapy, amphotericin B and fluconazole appear to be similarly effective. A comparative study of patients with AIDS-associated cryptococcal meningitis found that there was no significant difference in response between amphotericin B deoxycholate (AmBd) (40%) and fluconazole (34%).<sup>5</sup> Therapy with AmBd resulted in a faster time to first negative cerebral spinal fluid culture (42 days with AmBd vs 64 days with fluconazole), although this difference was not significant.

In the Collaborative Exchange of Antifungal Research (CLEAR) database, which included 106 patients with cryptococcosis, 67 of 101 (66%) evaluable patients had a favorable response, defined as a cure or improvement, to amphotericin B lipid complex.<sup>6</sup>

Because of the refractory nature of many fungal infections, combination antifungal therapy is being used increasingly to improve outcomes. A study of HIV-infected patients with cryptococcal meningitis found the

effects of combination therapy with amphotericin B and fluconazole to be additive.<sup>7</sup> This is consistent with in vitro and animal data.<sup>8,9</sup>

## What further workup is indicated in this stable patient?

Although the patient is clinically stable, further workup is indicated to monitor the infection and the response to therapy, especially since *Cryptococcus* can disseminate to various organs. Several options can be considered in this setting: chest computed tomography (CT), lumbar puncture, magnetic resonance imaging (MRI) of the brain, and susceptibility testing of the *C neoformans* isolate. In our patient, a chest CT scan with contrast was performed that showed a solitary nodule (Figure 1). Because of the propensity of *Cryptococcus* to disseminate, a lumbar puncture should typically be done to rule out CNS involvement. However, the diagnostic yield of a lumbar puncture is very low in patients with pulmonary cryptococcosis who present without CNS symptoms,<sup>3</sup> although the data are controversial.<sup>10</sup> Because our patient had thrombocytopenia (platelet count, 15,000 cells/ $\mu$ L), the primary team elected not to do a lumbar puncture, and, instead, a brain MRI was performed. The results were negative for meningeal enhancement or parenchymal brain lesions. Given these results and the results of the chest CT scan, it is likely that this patient had pulmonary cryptococcosis.

**Figure 1.**  
Chest Computed Tomography Scan With Contrast Showing a Solitary Nodule in Right Upper Lobe



We also conducted susceptibility testing of the *C neoformans* bloodstream isolate (Clinical and Laboratory Standards Institute™ method) in our patient. The results showed very low

minimum inhibitory concentrations for both amphotericin B and fluconazole. At this time, however, there is no established role of in vitro susceptibility testing for management of cryptococcal disease.<sup>11</sup>

Of note, bronchoalveolar lavage was not done, and sputum cultures were not obtained as the patient could not produce sputum. Additionally, a fine-needle aspirate was not done because of the patient's thrombocytopenia. In this patient with positive serum cryptococcal antigen and a solitary lung nodule who was receiving broad-spectrum combined antifungal therapy, we assumed that the possibility of pulmonary cryptococcosis was high and that it was reasonable to start therapy with a specific diagnosis.

**Two weeks into his therapy with lipid-based amphotericin B and fluconazole, the patient continues to improve. Follow-up blood cultures are negative, and he is tolerating the regimen well. However, the serum cryptococcal antigen titer remains unchanged (1:64).**

## What is the significance of a persistently positive serum cryptococcal antigen in this patient?

Detection of cryptococcal antigen in serum is extremely helpful in the diagnosis of infection with *C neoformans* but appears to have only a limited role in monitoring clinical response to therapy. Studies in this setting, however, are limited to AIDS-associated cryptococcal meningitis, and there are no data to date in non-HIV pulmonary cryptococcosis. Powderly et al reviewed cryptococcal antigen titers in patients with AIDS-associated cryptococcal meningitis who received amphotericin B or fluconazole for either acute disease or suppressive therapy. In this study, there was no correlation between outcome and changes in serum antigen titers.<sup>12</sup>

## Which follow-up tests are appropriate?

In this case, the patient is improving, but because he is at high risk for other potential problems, a follow-up CT scan is

appropriate. We repeated the CT scan to monitor the initial nodule. The follow-up CT scan showed a new right lower lobe mass (Figure 2). Based on these results, we conducted a repeat serum *Aspergillus* galactomannan assay; results came back positive on 2 consecutive days, with an optical density ratio of 1.5 ng.

**Figure 2.**

**New Right Lower Lobe Mass on Follow-up Computed Tomography**



### Is there cross-reactivity between *Cryptococcus* and *Aspergillus* in terms of the galactomannan assay?

Although the patient has a fairly well-documented *Cryptococcus* infection, positive results on the galactomannan assay are suggestive of an *Aspergillus* infection. However, a recent report described a case of a patient infected with HIV who had a lung biopsy consistent with *C neoformans* but also had positive results on the Platelia *Aspergillus* assay.<sup>13</sup> The investigators initiated testing of soluble antigens from 19 strains of *C neoformans* on the galactomannan assay. Results indicated that *C neoformans* galactoxylomannan contains epitopes that cross-react with the *Aspergillus* galactomannan. Thus, *Aspergillus* assay positivity in the HIV-infected patient was determined to be a result of cross-reactive antigens released by *C neoformans*.

At this point, then, we cannot be certain whether the patient is potentially developing a new infection with *Aspergillus* or whether the *Cryptococcus* infection is actually

worsening. It is possible that the patient has a dual infection with *Aspergillus* and *Cryptococcus*.

### What would you recommend now? Why?

Further diagnostics could be done at this time (eg, bronchoscopy) to look for an infection. In addition, it would probably be prudent to change antifungal therapy, given the fact that the CT scan showed a new right lower lobe mass and the patient had positive results on the galactomannan assay, which may be suggestive of a new developing *Aspergillus* infection. One option can be to change antifungal therapy, maintaining the lipid-based amphotericin B but switching from fluconazole to a broader-spectrum azole, such as voriconazole, which has activity against *Aspergillus*. Voriconazole also has preclinical evidence of activity against *Cryptococcus*, but data on clinical efficacy in this setting are lacking. A study evaluating voriconazole in 273 patients who were refractory to or intolerant of prior antifungal therapy included a subset of patients (n=18) with diagnosed *Cryptococcus* infection.<sup>14</sup> The trial suggested a relatively poor response to voriconazole treatment, with a satisfactory global response reported in only 7 of 18 (39%) patients. However, of the 11 patients who did not have a satisfactory outcome, 10 had stable disease at the end of treatment, based on stable serologic values.

In refractory cases, therapy with interferon-gamma (IFN- $\gamma$ ), granulocyte colony-stimulating factor (CSF), or granulocyte-macrophage CSF may be reasonable. These cytokine therapies enhance the activity of neutrophils and macrophages, thereby improving the host's immune defense against the fungal infection. Dignani et al recently reported a case series of 4 patients with leukemia who had refractory invasive candidiasis or trichosporonosis. Patients were treated with IFN- $\gamma$  plus a CSF for 1.5 to 5 months, and therapy resulted in a clinical response for each patient.<sup>15</sup>

### What happened to the patient?

Since the patient was reluctant to have a bronchoscopy and in view of the fact that the patient was to be transferred close to home, a bronchoscopy was not performed. We did, however, substitute voriconazole for fluconazole. Four weeks later, the patient continues to be stable. A follow-up chest CT scan at this time was much improved. A repeat galactomannan assay was not done; however, serum cryptococcal antigen titer is 1:16. Patient remains cytopenic with active chronic lymphocytic leukemia (CLL) and is taking voriconazole for secondary prophylaxis.

In summary, this was an interesting case of a heavily immunosuppressed febrile CLL patient with fungemia due to *C neoformans*. Therapy was initiated with caspofungin, but when it was determined that the infection was due to *C neoformans*, we discontinued therapy with caspofungin (which has no activity against this yeast) and initiated a lipid-based amphotericin B and fluconazole. Further diagnostics revealed a new right lower lobe mass and positive results on the galactomannan assay. Although *Cryptococcus* can result in false positives on the galactomannan assay, it is very possible that this patient had a dual infection with *Cryptococcus* and *Aspergillus*. Since the patient lived close to the hospital, he was discharged on the combination of a lipid-based amphotericin B and voriconazole. He received the lipid-based amphotericin B for 1 month (total dose, 12 g) without toxicity. Currently, he remains on oral voriconazole as secondary prophylaxis.

CLL continues to be the prototype of severe, pleiotropic immune defects. Patients with CLL are therefore highly susceptible to fungal infections, and less common fungal infections may be more common in these patients. The need for broad-spectrum antifungal coverage is a common real-life scenario in these patients.

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