Journal of Infection (2005) **51**, e181–e183

www.elsevierhealth.com/journals/jinf

CASE REPORT

Cryptococcal fungemia in a neutropenic patient with AIDS while receiving caspofungin

Prashant Malhotra[a], Sanjiv S. Shah[a], Mark Kaplan[a,b], Joseph P. McGowan[a,c,*]

[a]*North Shore University Hospital, Manhasset, NY, USA*
[b]*New York University School of Medicine, New York, USA*
[c]*Albert Einstein College of Medicine, New York, USA*

Accepted 4 January 2005

KEYWORDS
HIV/AIDS;
Cryptococcus;
Caspofungin;
Neutropenia

Abstract Empiric choice of anti-fungal therapy in febrile neutropenia should be based upon a host's susceptibility to specific fungal pathogens. We present a case of a patient with multiple risk factors for fungemia including HIV infection, Hodgkin's disease, corticosteroid use and chemotherapy-induced neutropenia who developed disseminated cryptococcal infection while receiving caspofungin.

Introduction

Fungal infections are an important cause of morbidity and mortality in patients with impaired immunity.[1] Host immune status should be an important consideration when planning interventions for prophylaxis and treatment of fungal infections. Amphotericin B has been the anti-fungal agent most extensively used in the setting of febrile neutropenia.[2] The availability of caspofungin may provide an effective and possibly less toxic alternative to amphotericin B; however, the anti-fungal spectrum of these two agents is different.[3] Caspofungin, like other echinocandins, is not active against basidiomycetous yeasts, such as *Cryptococcus neoformans*, *Trichosporon* species and *Rhodotorula*.[4] In the era of potent anti-retroviral therapy accompanied by immune reconstitution, HIV-infected patients are receiving aggressive chemotherapy for both HIV-associated and other malignancies.[5,6] Following anti-cancer chemotherapy, patients with febrile neutropenia and HIV infection may differ from uninfected individuals in their susceptibility to certain fungal infections, which may affect the choice of empiric anti-fungal therapy. We report a case of an HIV-infected patient with neutropenic fever after receiving chemotherapy for Hodgkin's disease who developed cryptococcemia on empiric caspofungin.

Case review

A 50-year-old male presented to our institution with a 1 day history of high-grade fever associated with

* Corresponding author. Address: Division of Infectious Diseases, North Shore University Hospital, 300 Community Drive, Manhasset, New York 11030, USA. Tel.: +1 516 562 4280; fax: +1 516 562 2626.
E-mail address: jmcgowan@nshs.edu (J.P. McGowan).

0163-4453/$30.00
doi:10.1016/j.jinf.2005.01.002

fatigue but no other localizing signs. The patient had been diagnosed with stage IV mixed cellularity type Hodgkin's disease (with bone marrow involvement) 3 months prior to admission. One week before his admission, he had received his third cycle of doxorubicin/bleomycin/vinblastine/dacarbazine.

He was diagnosed with HIV infection in 1994 and was coinfected with hepatitis C. He had no history of opportunistic infections. His anti-retroviral regimen at the time of hospital admission consisted of tenofovir, lamivudine and ritonavir-boosted atazanavir. Prior to the initiation of chemotherapy his CD4 count was 270 cells/mm^3 and an HIV-1 viral load was <50 copies/ml. His lowest CD4 count was 20 cells/mm^3 (CD4 percentage was 17) during his hospital admission.

His initial physical examination was remarkable only for a temperature of 102.5 F. On admission, he had a total white cell count of 0.4×10^9 cells/l. An extended metabolic panel was normal except for mildly elevated transaminases. Chest roentogram revealed minimal bibasilar linear atelectasis but no acute infiltrate. He was initiated on intravenous piperacillin/tazobactam and gentamicin but his fever persisted. On the fifth hospital day, he developed dyspnoea and basal crackles were heard bilaterally on chest auscultation. Concurrent chest radiography demonstrated indistinct biapical infiltrates with associated nodularity; findings that were confirmed on a thoracic CT scan. He was empirically started on primaquine and clindamycin to cover *Pneumocystis* pneumonia (he was allergic to trimethoprim-sulfamethoxazole) and underwent bronchoscopy. Special stains for *Pneumocystis*, and stains and cultures for acid-fast organisms, fungi and bacteria from a broncheoalveolar lavage were negative. A serum cryptococcal antigen was negative. Blood cultures from admission were negative for growth. The patient continued with febrile neutropenia and intravenous caspofungin (70 mg loading dose followed by 50 mg daily) was added on the eighth day of hospitalisation. The lung infiltrates were felt to be secondary to bleomycin-induced lung toxicity and he was empirically started on intravenous steroids on the tenth hospital day. The patient became afebrile 1 day later. Pentoxifylline was added to taper his steroid dosage. Repeat blood cultures continued to show no growth. His oxygen requirements steadily decreased and he improved clinically over the next 2 weeks while remaining hospitalised.

On the twenty-fifth hospital day, the patient became severely dyspnoeic while on steroids and pentoxifylline. A thoracic CT scan showed increased reticulonodular opacities with a small pneumothorax and pneumomediastinum. There was no evidence for pulmonary embolism. A repeat bronchoscopy was performed which again was negative for *Pneumocystis*, bacterial, mycobacterial and fungal pathogens. Concurrent blood cultures grew *C. neoformans* and a previously negative serum cryptococcal antigen became positive at a titre of 1:128. Cerebrospinal fluid cryptococcal antigen and fungal cultures were negative. The patient was successfully treated with intravenous fluconazole for 6 weeks. His fever and dyspnoea completely resolved 1 week after the initiation of azole therapy. Repeat blood cultures prior to discharge showed no growth. Maintenance oral fluconazole was continued after completion of intravenous therapy.

Discussion

HIV-infected patients with neutropenic fever following anti-cancer chemotherapy are susceptible not only to the usual fungal pathogens identified in this setting (such as *Candida* species and *Aspergillus* species) but may also be prone to infection with additional fungal organisms such as *Cryptococcus*, *Histoplasma* and *Pneumocystis*, among others. Increased susceptibility to these opportunistic pathogens is due to HIV-associated T-helper cell dysfunction, which impairs cell-mediated immunity. Cellular immunity mediates the activation of alveolar macrophages that phagocytose inhaled yeast cells of *C. neoformans*.[7] Neutrophils and monoctye-dervied macrophages are capable of in vitro killing of *C. neoformans* and may control *C. neoformans* infection in the bloodstream.[7,8] Furthermore, this patient was treated with corticosteroids, which also increase the risk for cryptococcosis by impairing neutrophil chemotaxis, inducing lymphopenia and depressing cell-mediated immunity.[7] Hodgkin's disease and other lymphoproliferative disorders (such as chronic leukaemia) are independently associated with the development of cryptococcal infections.[7,9] Our patient was also receiving pentoxifylline, which may decrease secretion of the proinflammatory cytokine tumour necrosis factor-α (TNF).[10] While cryptococcal infections have not been reported in patients receiving pentoxifylline, there have been cases of pulmonary *Cryptococcus* in patients receiving the anti-TNF monoclonal antibody infliximab.[11] Even though patients receiving anti-cancer chemotherapy can be both lymphopenic and neutropenic, the absence of disseminated cryptococcosis as a common fungal pathogen in the febrile neutropenic host is likely due to the inadequate duration of

T-cell deficiency. However, purine analogs, although not used in our patient, can cause leucopenia, in particular profound and prolonged lymphopenia, and have been associated with a variety of opportunistic infections including cryptococcosis.[12]

Anti-fungal treatment is instituted empirically in chemotherapy-induced neutropenic patients who continue to be febrile on broad-spectrum antibiotics.[2] Although amphotericin B is often used in such patients, recent separate studies in this setting have favourably compared voriconazole and caspofungin, respectively, with liposomal amphotericin B.[3,13] Encouragingly, the occurrence of breakthrough invasive fungal pathogens was not common in these studies and no cases of *C. neoformans* were identified. However, neither study described whether patients with HIV infection were excluded or, if not specifically excluded, the proportion of patients with HIV infection in either arm. Walsh et al. reported that febrile neutropenic patients who received caspofungin had improved short-term survival, similar incidence of breakthrough fungal infection and a lower rate of nephrotoxicity compared with those who received amphotericin B.[3] Caspofungin is an echinocandin that inhibits the synthesis of 1, 3-beta-D-glucan in the fungal cell wall of *Candida* species and *Aspergillus* species. However, caspofungin is not active against *C. neoformans*. Echinocandin resistance may be due to the presence of a structurally different glucan synthase in *C. neoformans*, poor drug penetration or calcineurin dependent regulation of 1, 3-beta-D-glucan synthase expression.[4,14]

This case illustrates that *C. neoformans* fungemia can occur in the febrile neutropenic patient particularly if the host's cell-mediated immunity is also impaired. Clinicians should be aware that the choice of an empiric anti-fungal agent in the neutropenic patient with fever should be influenced by the individual's susceptibility to certain fungal pathogens.[15] Caspofungin, which is not active against *C. neoformans*, should be used with caution, if at all, in HIV-infected patients with chemotherapy-induced neutropenia. Amphotericin B and its lipid formulations, and possibly voriconazole, may be more appropriate in these patients.

References

1. Vartivarian SE, Anaissie EJ, Bodey GP. Emerging fungal pathogens in immunocompromised patients: classification, diagnosis, and management. *Clin Infect Dis* 1993;(Suppl 2): S487–S91.
2. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;**34**:730–51.
3. Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004;**351**: 1391–402.
4. Denning DW. Echinocandin antifungal drugs. *Lancet* 2003; **362**:1142–51.
5. Sparano JA. Human immunodeficiency virus associated lymphoma. *Curr Opin Oncol* 2003;**15**:372–8.
6. Hartmann P, Rehwald U, Salzberger B, Franzen C, Diehl V. Current treatment strategies for patients with Hodgkin's lymphoma and HIV. *Expert Rev Anticancer Ther* 2004;**4**: 401–10.
7. Mitchell TG, Perfect JR. Cryptococcosis in the era of AIDS—100 years after the discovery of *Cryptococcus neoformans*. *Clin Microbiol Rev* 1995;**8**:515–48.
8. Mednick AJ, Feldmesser M, Rivers J, Casadevall A. Neutropenia alters lung cytokine production in mice and reduces their susceptibility to pulmonary cryptococcosis. *Eur J Immunol* 2003;**33**:1744–53.
9. Kaplan MH, Rosen PP, Armstrong D. Cryptococcosis in a cancer hospital. *Cancer* 1977;**39**:2265–74.
10. Ostrosky-Zeichner L, Soto-Hernandez JL, Angeles-Morales V, et al. Effects of pentoxifylline or dexamethasone in combination with amphotericin B in experimental murine cerebral cryptococcosis: evidence of neoroexcitatory pathogenic mechanisms. *Antimicrob Agents Chemother* 1996;**40**: 1194–7.
11. Hage CA, Wood KL, Winer-Muram HT, Wilson SJ, Sarosi G, Knox KS, et al. Pulmonary cryptococcosis after initiation of anti-tumor necrosis factor-α therapy. *Chest* 2003;**124**: 2395–7.
12. Samonis G, Kontoyiannis DP. Infectious complications of purine analog therapy. *Curr Opin Infect Dis* 2001;**14**:409–13.
13. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002;**346**:225–34.
14. Del Poeta M, Cruz MC, Cardenas ME, Perfect JR, Heitman J. Synergistic antifungal activities of bafilomycin A1, fluconazole and the pneumocandin MK0991/caspofungin acetate (L-743,873) with calcineurin inhibitors FK506 and L-685,818 against *Cryptococcus neoformans*. *Antimicrob Agents Chemother* 2000;**44**:739–46.
15. Singh N. Trends in the epidemiology of opportunistic fungal infections: predisposing factors and the impact of antimicrobial use practices. *Clin Infect Dis* 2001;**33**:1692–6.