

# Breakthrough *Candida krusei* Fungemia during Fluconazole Prophylaxis followed by Breakthrough Zygomycosis during Caspofungin Therapy in a Patient with Severe Aplastic Anemia Who Underwent Stem Cell Transplantation

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**We report a case of breakthrough invasive zygomycosis in a stem cell transplant recipient who was receiving caspofungin for treatment of a breakthrough *Candida krusei* fungemia that occurred during fluconazole prophylaxis. Also, patients receiving the echinocandin caspofungin remain at risk for pathogens, such as zygomycetes, that are intrinsically resistant to this agent.**

## CASE REPORT

A 16-year-old girl was diagnosed with severe aplastic anemia in January 2000. She was unsuccessfully treated with cyclosporine and prednisone in Romania, and in May 2003, she was admitted to our center for an allogeneic bone marrow transplantation from her HLA-compatible sister. The patient received fludarabine and antilymphocyte serum as conditioning for the transplant. As part of the transplantation protocol, cyclosporine therapy was started as prophylaxis against graft-versus-host disease. Neutrophil and platelet engraftments were obtained on days 13 and 32 posttransplant, respectively. In September 2003, the patient developed fever, two right pulmonary lesions, and pleural effusion. A diagnosis of pulmonary tuberculosis was made on the basis of *Mycobacterium tuberculosis* isolated from the bronchoalveolar lavage fluid, and a specific treatment with isoniazid, rifampin, and pyrazinamide was started. During the subsequent months, the clinical course was complicated by recurrent cytomegalovirus reactivations which required antiviral treatment with ganciclovir, foscarnet, and cidofovir. In October 2003, in consideration of the underlying mycobacterial infection and of the absence of any signs of graft-versus-host disease, immunosuppressive therapy with steroids and cyclosporine was completely discontinued. In December, a graft failure was documented and bone marrow drug toxicity was hypothesized; it was, therefore, decided to discontinue all antimicrobial treatments, including the antitubercular drugs. On 26 December, the patient was again admitted with febrile neutropenia, and an antibacterial therapy with ceftriaxone plus amikacin was started. At that time, the patient was not receiving any immunosuppressive therapy, was under granulocyte colony-stimulating fac-

tor treatment, and was under antiviral and antifungal prophylaxis with acyclovir and fluconazole (200 mg intravenously daily). A total-body computed tomography scan documented multiple micronodular pulmonary lesions while paranasal sinuses were unremarkable. Due to the persistence of fever, therapy was changed to piperacillin-tazobactam plus teicoplanin, and antimycobacterial therapy with isoniazid plus rifampin was newly inserted, although sputum examination was negative for acid-fast bacilli. However, multiple blood cultures and sputum cultures demonstrated the presence of *Candida krusei* (identification was performed by the VITEK system; Bio Merieux Italia, Rome, Italy), and caspofungin therapy, 70 mg the first day and 50 mg the subsequent days, was given to the patient. Blood cultures became negative without central venous catheter removal, fever disappeared after 6 days of caspofungin therapy, and radiologic findings progressively improved. It was decided, due to the persistent cytopenia, to perform a second hematopoietic stem cell transplantation on the patient, and on 13 February 2004, she received peripheral blood stem cells from her HLA-compatible sister. On 17 February 2004, 27 days after the start of caspofungin, the patient developed dull headache, nasal discharge, and maxillary tenderness. A CT scan documented sphenoidal and maxillary mass lesions with erosion of the sinus walls and a large pulmonary infiltrate. A nasal discharge culture grew cottony white colonies after 24 h of incubation. The isolate grew rapidly and filled the petri dish within 3 days. The colonies matured and became gray after 3 to 4 days. Tease mount was prepared and showed broad, nonseptate hyphae with right-angled branching, long and branched, or unbranched sporangiothecae bearing terminal, round, spore-filled sporangia. No rhizoids were observed. According to these features, the isolate was identified as a *Mucor* species strain. Liposomal amphotericin B therapy (5 mg/kg/day) was started in place of caspofungin therapy. Within a few days, a slight improvement of the paranasal infectious signs and symptoms (reduction of head-

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ache and maxillary tenderness) was observed; nonetheless, the patient died on 6 March due to *Pseudomonas aeruginosa* septic shock while still profoundly neutropenic.

The recent availability of the azole voriconazole and the echinocandin caspofungin has significantly improved the therapeutic armamentarium for severe fungal infections in immunocompromised patients. Although voriconazole and caspofungin have proven to be highly effective against *Aspergillus* species and *Candida* species, both drugs have a limited activity against pathogenic zygomycetes. This could explain the recent observation of breakthrough zygomycosis in patients under voriconazole treatment, particularly those receiving prolonged prophylaxis with the azole (4–7, 9, 10). To our knowledge, this is the fourth case of zygomycosis during treatment with caspofungin so far reported (8, 13), and a few cases of deep breakthrough infection by other pathogens intrinsically resistant to the echinocandin, such as *Fusarium* species and *Trichosporon* species, have also been described (3, 13). The occurrence of breakthrough infections by resistant fungal pathogens is a well-known phenomenon in immunocompromised patients receiving azole treatment. Fluconazole and itraconazole have been associated with the emergence of infections by resistant *Candida* species, such as *C. krusei* and *C. glabrata*, and some recent reports seem to show that patients under treatment with the new azole voriconazole can be at risk of infections with organisms that are always resistant (e.g., zygomycetes) or sometimes resistant (e.g., *C. glabrata*, *Acremonium* species, or *Fusarium* species) to the drug (2, 4–7, 9, 10).

The phenomenon of breakthrough fungal infections, particularly zygomycosis, has been emphasized in the literature as a potential limit of the new antifungal treatment options, especially voriconazole. On the other hand, according to the cumulative data of the six largest randomized studies of empirical antifungal therapy in patients with febrile neutropenia (1, 11–15), breakthrough zygomycosis occurred in 2 of the 556 patients receiving caspofungin, 2 of the 415 patients receiving voriconazole, and only 1 of the 2,286 patients receiving any formulation of amphotericin B. In our opinion, the apparent slightly higher incidence of breakthrough zygomycosis under voriconazole and caspofungin empirical therapies compared to amphotericin B is not an unexpected event, but it simply reflects the different antimicrobial spectra of the individual drugs. Selective pressure due to the prolonged use of the antifungal drug has been supposed to explain the apparently increased number of cases of zygomycosis observed in patients receiving prolonged voriconazole prophylaxis (4, 6, 9, 10); however, a real increase in the incidence of these rare fungal infections has until now not been demonstrated. On the other hand, literature data seem to suggest that subjects with severe, prolonged immunosuppression who receive long-term antifungal treatments, such as our hematopoietic stem cell transplantation patient, are at an increased risk of breakthrough fungal infections.

Although a significant impact of the use of the new antifungal drugs in the epidemiology of some rare invasive mycoses, including zygomycosis, cannot at present be documented, clinicians should be aware of the potential risk of breakthrough infections caused by several resistant fungi for patients with severe, prolonged immunosuppression who are receiving long-term antifungal drugs, including caspofungin.

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