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CASE REPORT

Emergence of *Candida albicans* fungemia during voriconazole therapy

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Nowadays, the primary choice of therapy for infections due to *Candida* species is still fluconazole.[1,2] However, several reports describing in vitro and clinical resistance to fluconazole developing during azole therapy have been published in the last years.[3,4] This concern have resulted in the continued search for new agents with increased potency against *Candida*. Voriconazole, a second-generation triazole, have demonstrated excellent potency and broad-spectrum activity against all *Candida* species either in vitro[5] and in vivo.[6] Unfortunately, since all azoles act on the same molecular target, cross-resistance was suspected when in vitro studies have shown a reduced susceptibility to voriconazole for fluconazole-resistant isolates compared to fluconazole-susceptible isolates.[7,8] However, *Candida* resistance to voriconazole was never described in clinical practice. As our knowledge, we present here the first reported case of *Candida albicans* bloodstream infection that emerged during voriconazole therapy.

A 27-year-old woman, with no past medical history, was diagnosed with severe aplastic anemia in September 2002. She was treated during 4 months with anti-thymocyte globulin, corticosteroids, cyclosporine and granulocyte-colony stimulating factor, but did not respond. In January 2003, low-grade fever developed and persisted despite empiric antibiotic treatment with imipenem, ofloxacin and teicoplanin. Because of abnormal liver function tests, ultrasound and abdominal CT scan were performed and revealed multiple focal lesions in the liver and spleen. Blood cultures were negative but antibodies to *C. albicans* mannan detected by the commercially available Platelia *Candida*-specific Ab test (Bio-Rad Laboratories) were positive, and no deep-tissue biopsy was undertaken. Oral voriconazole 400 mg bid was added to the antibiotic regimen for empiric treatment of probable hepatosplenic fungal infection. Subsequently, fever and lesions in serial imaging studies regressed. One month later, the patient underwent conditioning regimen of anti-T-lymphocyte globulin for 5 days and cyclophophamide for 4 days before allogeneic bone marrow transplantation from an HLA-matched unrelated donor. Post-transplant graft-versus-host disease prophylaxis was achieved with cyclosporine A plus

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short-course methotrexate. During this time, the patient was nursed in a protective environment. On day 6, despite broad-spectrum antibiotics and voriconazole, she developed fever, tachycardia and change in mental status. Three blood cultures revealed a *C. albicans* infection for which caspofungine 50 mg/day was added to the patient's treatment. In vitro susceptibility testing determined by Etests method demonstrated resistance to fluconazole (MIC = 256 μg/ml) and elevated MIC for voriconazole (> 32 μg/ml) with trailing phenomenon. No bacterial, mycobacterial or viral co-infection was diagnosed. On day 7, she developed progressive respiratory failure, hypotension and oliguria, and was transferred to the medical ICU. Her chest radiograph demonstrated diffuse bilateral infiltrates. Mechanical ventilation was initiated with a respiratory rate of 25 breaths/min, a positive end-expiration pressure of 10 mmHg, a maximal inspiratory pressure of 35 mmHg, and an inspiratory oxygen fraction of 100%. For blood pressure support, she received IV norepinephrine and dobutamine after catheter replacement. However, persistent sepsis resulted in multiorgan failure and death on the third ICU day.

The development of secondary resistance to fluconazole treatment has been most commonly encountered in HIV-infected patients with oropharyngeal candidiasis who are receiving prolonged treatment with fluconazole.[9] Recently, the same resistance was reported in bone marrow transplant recipients being administered long-term fluconazole prophylaxis.[10] Because voriconazole is active in vitro against various yeasts and molds, it has become the drug of choice for empiric treatment of fungal infections in immunocompromised patients. However, there has been relatively little experience with the use of this agent, as compared with fluconazole. Moreover, it is important to note that MIC breakpoints have not yet been established for voriconazole, although preliminary interpretive category of susceptible by use of an MIC threshold of ≤1 μg/ml may be supported by pharmacokinetic and pharmacodynamic profiles.[11] Our case report suggests that in the treatment of disseminated candidiasis, reduced susceptibility or clinical resistance to voriconazole may develop during therapy. Further studies are needed to identify the molecular or clinical mechanisms for such resistance. A potential limitation of this case is that we have no pre-treatment values, but it is very unlikely that our patient was infected with a fluconazole resistant strain that was cross-resistant to voriconazole. Meanwhile, since *C. albicans* can develop resistance to azoles during therapy and since cross-resistance to other azoles is likely to occur, physicians should be aware of the consequences of substituting one azole compound for another if a patient does not have a response to the initial therapy.

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