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Disseminated Fusariosis Occurring in Two Patients Despite Posaconazole Prophylaxis▽

Prithviraj Bose,[1] Hiral D. Parekh,[2] Jennifer L. Holter,[1] and Ronald A. Greenfield[2]*

Section of Hematology/Oncology[1] and Department of Internal Medicine,[2] University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

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Posaconazole is widely used for prophylaxis against invasive fungal infections in patients undergoing myeloablative therapy. Disseminated fusariosis is a serious invasive mold infection in such patients. Preclinical and clinical studies indicate activity of posaconazole against *Fusarium*. We describe two cases of disseminated fusariosis that occurred despite posaconazole prophylaxis.

CASE REPORTS

Case report 1. A 47-year-old female was diagnosed with acute myelogenous leukemia (AML) 6 years after a failed allogeneic haploidentical sibling donor allogeneic hematopoietic stem cell transplant (HSCT) for sickle cell anemia. She began standard induction chemotherapy with cytarabine and idarubicin and was placed on posaconazole (200 mg by mouth three times daily) for antifungal prophylaxis. She was also started on vancomycin for *Corynebacterium striatum* bacteremia. Piperacillin-tazobactam was empirically added 10 days later for persistent fever and was changed to ceftazidime after another 4 days because she did not defervesce. Following this, she became afebrile for 2 days, only to develop a low-grade fever again. Blood cultures remained negative after initiation of antibacterial therapy. Three weeks after the initiation of chemotherapy, the patient developed multiple tender, erythematous papular skin lesions scattered over her trunk, extremities, and face. Biopsy of these showed numerous intravascular/perivascular fungal hyphae, consistent with disseminated fungal infection. At the same time, blood from her indwelling intravenous port grew *Fusarium* species with MICs of 4 μg/ml, 2 μg/ml, and 4 μg/ml for amphotericin B (AmB), posaconazole, and voriconazole, respectively (by the broth microdilution method). Posaconazole was stopped, and she was treated with liposomal AmB (5 mg/kg of body weight intravenously [i.v.] every 24 h) and voriconazole (6 mg/kg i.v. for two doses 12 h apart, followed by 4 mg/kg every 12 h). She also received one granulocyte transfusion as part of the Reduction of Infections in Neutropenia with Granulocytes (RING) study. She received granulocyte colony-stimulating factor (G-CSF) briefly, and it and vancomycin and ceftazidime were stopped when the neutropenia resolved. Her skin lesions began to heal with crusting, blood cultures became and remained negative, and she became afebrile. A repeat bone marrow biopsy showed no evidence of persistent AML, and she was discharged on liposomal AmB and oral voriconazole 3 weeks after the diagnosis of disseminated fusariosis. She was readmitted 17 days later for consolidation chemotherapy. AmB was stopped due to worsening renal function, and voriconazole was continued. Chemotherapy with cytarabine was administered once her renal function stabilized, and she was discharged. Unfortunately, 11 days after her second hospital discharge, she presented with hypotension, dyspnea, dehydration, and renal failure, and she died within 24 h of overwhelming pneumococcal septic shock.

Case report 2. A 42-year-old male was diagnosed with AML after presenting with a scrotal abscess, extreme leukocytosis, anemia, and thrombocytopenia. After emergent leukapheresis, he underwent incision and drainage of scrotal and dental abscesses with complete maxillary dental extraction and was placed on imipenem, metronidazole, and vancomycin based on the results of susceptibility testing on cultures from his scrotal abscess (*Bacteroides* spp., coagulase-negative staphylococci, diphtheroids, and peptostreptococci). Vancomycin and metronidazole were discontinued after 13 and 5 days, respectively, whereas imipenem was continued. Standard induction chemotherapy for AML was administered with cytarabine and idarubicin. He received fluconazole (200 mg orally daily) for 7 days for unidentified yeast (not *Cryptococcus*) cultured from his sputum and *Candida albicans* cultured from his dental abscesses. After that, he was placed on posaconazole (200 mg by mouth three times daily) for antifungal prophylaxis. Reinduction with high-dose cytarabine was attempted after a day 14 bone marrow biopsy showed persistent AML. Two weeks after starting posaconazole, the patient complained of pain and swelling in the left nasolabial region. Culture from a nasal swab grew *Fusarium* species. Posaconazole was then stopped, and he was placed on liposomal AmB (5 mg/kg every 24 h). Imipenem was changed to cefepime plus ciprofloxacin after blood cultures grew *Pseudomonas aeruginosa* resistant to imipenem, and G-CSF was added. He also developed a pimple-like lesion on his left chest that was biopsied, cultures of which grew *Fusarium*. Voriconazole (6 mg/kg i.v. for 2 doses 12 h apart, followed by 4 mg/kg every 12 h) was then substituted for AmB. Shortly thereafter, vancomycin was resumed due to *Enterococcus faecalis* bacteremia. The patient underwent maxillary antrostomy and left inferior turbinate resection due to persistent left

* Corresponding author. Mailing address: Department of Internal Medicine, University of Oklahoma Health Sciences Center, 920 Stanton L Young Blvd., WP-1360, Oklahoma City, OK 73104. Phone: (405) 271-5882. Fax: (405) 271-1476. E-mail: ronald-greenfield@ouhsc.edu.

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maxillary sinusitis, and cultures of his nasal tissues again grew *Fusarium* species, with MICs of 2 μg/ml for AmB and voriconazole but >16 μg/ml for posaconazole (by the broth microdilution method). Invasive fungal sinusitis was histopathologically confirmed in biopsy specimens. The antibacterials were stopped, and voriconazole was continued. Second-look endoscopic sinus surgery with exploration and debridement of the left nasal cavity again showed hyphae in the necrotic debris. Salvage chemotherapy with cladribine, cytarabine, and mitoxantrone with G-CSF priming (CLAG-M) was administered due to persistent AML. After this, the patient developed neutropenic fever and septic shock. Blood cultures grew *Pseudomonas aeruginosa* again. Vancomycin, ciprofloxacin, and AmB were all restarted, and ceftazidime was added, while voriconazole and G-CSF were continued. Computerized tomography suggested invasive fungal disease in the nose and sinuses and also showed multiple brain lesions. Despite all efforts, his clinical condition progressively deteriorated; he remained profoundly pancytopenic and died a few days later.

The epidemiology of invasive fungal infections (IFI) is changing (5, 8). *Fusarium* species are important plant pathogens that can cause a wide array of human infections. Keratitis and onychomycosis are the most common infections in immunocompetent hosts, but immunocompromised patients may develop endophthalmitis, sinusitis, pneumonia, skin lesions, fungemia, and disseminated infections. Patients with prolonged and profound neutropenia and/or severe T-cell immunodeficiency are at high risk for disseminated fusariosis (6). Indeed, among immunocompromised patients, invasive fusariosis represents the second most common invasive mold infection (after aspergillosis). In a retrospective review of 84 patients with hematologic malignancies and invasive fusariosis, multivariate predictors of poor outcome were persistent neutropenia and use of corticosteroids. Only 18 patients (21%) remained alive 90 days after the diagnosis of fusariosis, no patient with both risk factors survived, and the actuarial survival rate for patients with persistent neutropenia was only 4% (7). Treatments include AmB, voriconazole, and posaconazole, complemented by removal of infected catheters, surgical debulking of infected tissues when feasible, G-CSF treatment, and G-CSF-stimulated granulocyte transfusions (6).

Posaconazole is an expanded-spectrum triazole antifungal recommended by the National Comprehensive Cancer Network (NCCN) for prophylaxis against fungal infections in patients undergoing chemotherapy for AML or myelodysplastic syndrome (MDS) who are or are anticipated to be neutropenic and in HSCT recipients with graft-versus-host disease (GVHD) (11), based on two large, randomized phase III controlled trials (1, 12). Its broad spectrum of *in vitro* activity, oral route of administration, lack of a need for dose adjustment in patients with renal or hepatic dysfunction, and safety profile have made posaconazole a popular choice for prophylaxis (10). However, the emergence of resistant mold infections is almost inevitable (5).

There are reports of the successful treatment of fusariosis with posaconazole. In the largest series, 21 patients with proven or probable fusariosis, who had failed or were intolerant of standard antifungal therapy, received salvage treatment with posaconazole (9). An underlying hematologic malignancy was present in 76%. A successful outcome occurred in 10 (48%), which contrasts sharply with the 21% 90-day survival rate seen in the first-line setting (7), suggesting that these patients may have had a better prognosis simply by their surviving long enough to receive a second treatment (6).

The absorption of posaconazole can be quite unpredictable, with large variations in bioavailability based on the number of daily doses, fed versus fasting state, and meal composition (10). A case of disseminated fusariosis that developed and progressed on posaconazole was reported (3). In that case, successful therapy was achieved by changing therapy because subtherapeutic posaconazole levels were measured even at the most bioavailable 200-mg four-times-daily dose. Indeed, therapeutic monitoring has been suggested for posaconazole, and a specific recommendation has been proposed by the FDA but is not part of the current FDA-approved labeling (10) or common practice. Evaluation of our cases is limited by the lack of therapeutic drug monitoring.

Meta-analyses of antifungal prophylaxis in patients with hematologic malignancies show that prophylaxis decreases IFI and IFI-related mortality but not overall mortality (4). The large trial of posaconazole prophylaxis in HSCT recipients with GVHD (12) noted the emergence of *Candida* species isolates with reduced *in vitro* susceptibility to posaconazole and/or other triazoles. Our experience shows that life-threatening *Fusarium* infections may occur in immunocompromised patients on prophylactic posaconazole. As such, preemptive and empirical therapy approaches to the management of IFI may remain warranted in patients receiving posaconazole prophylaxis (2).

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