

SUCCESSFUL VORICONAZOLE THERAPY OF DISSEMINATED *FUSARIUM SOLANI* IN THE BRAIN OF A NEUTROPENIC CANCER PATIENT

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Introduction

Although *Aspergillus* remains the most common of the opportunistic molds in patients with hematologic malignancies, disseminated *Fusarium* infection is increasingly encountered as more aggressive chemotherapeutic regimens and bone marrow transplants lead to prolonged neutropenia.¹⁻¹¹ Most frequently pathogenic to man is *F solani*, followed by *F oxysporum*, *F verticillioides*, and *F proliferatum* as the next most common¹² of a dozen other species that have been documented. Still other species are significant as pathogens of plants and animals. A fatal leukoencephalomalacia of horses is caused by fumonisins that contaminate corn and corn byproducts while in the field.¹³ The fungus is ubiquitous in the soil and has recently been found in water and wet surfaces within a hospital with known fusarial infections.¹⁴ However, some cancer hospital epidemiologists have concluded that the external environment is the more likely source of infection to patients.¹⁵ Entry is either airborne or through a breakdown in the skin barrier,¹⁰ but central venous catheters should not be underestimated as portals of entry.^{5,16}

Fusarium infection in patients with prolonged neutropenia carries a poor prognosis. Current treatment is limited by the relative resistance of the fungus to standard antifungals such as amphotericin B, as well as by their associated toxicity. Less nephrotoxic lipid formulations of ampho-

tericin B have recently been introduced and combined with other antifungal agents. Nevertheless, mortality from infection can still reach 80%.^{17,18}

We present a patient with leukemia, prolonged neutropenia, and disseminated cerebellar *Fusarium* infection that was successfully treated with a new triazole, voriconazole. Prophylactic use of this compound also prevented a recurrence of infection during a neutropenic relapse following treatment of the neoplasm.

Case Report

The patient was a 76-year-old farmer from south Florida with a history of advanced prostate cancer that was treated in the previous year by irradiation. He was admitted to our institute and acute myelogenous leukemia was diagnosed. Standard induction chemotherapy was followed by consolidation therapy. While he was neutropenic, an ulcer developed between the fourth and fifth toes, accompanied by cellulitis and lymphangitis of the foot. A specimen from the ulcer revealed a filamentous fungus and grew *Fusarium* infection. A shave biopsy of erythematous papules and pustules on the left arm showed hyphal elements and likewise grew *Fusarium* infection in culture. Amphotericin B lipid complex (5 mg/kg per day) for 6 weeks was followed by 200 mg of itraconazole twice daily, also for 6 weeks. The neutropenia and the cutaneous lesions resolved over the fol-

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lowing week. However, relapse of his leukemia occurred 6 months later, and he was admitted for high-dose chemotherapy. He had a 1-week duration of fever, diarrhea, and nausea but no sinus congestion or cough. Because of his history of *Fusarium* infection, he was treated prophylactically with itraconazole 200 mg twice daily. On day 3 of hospitalization, he received high-dose cytotoxic chemotherapy consisting of mitoxantrone, etoposide, and cytarabine (MEC). Subsequently, the patient's total white blood cell (WBC) count fell to $.05 \times 10^9/L$, where it remained until the 25th day of hospitalization.

On day 8 of neutropenia, blood cultures from the Hickman catheter site grew *Pseudomonas aeruginosa*. Computed tomography (CT) scan of the chest also revealed a left-sided pleural effusion. In addition to antipseudomonal antibodies, vancomycin was prescribed and 5 mg/kg of amphotericin B lipid complex (ABLC) was added to the antifungal itraconazole regimen. All subsequent blood cultures and urine specimens were negative. After 4 days, the patient was unable to ambulate, again having pain in his foot. There was an erythematous macular rash with red streaks without calor in its distal aspect that was reminiscent of the fusarial infection diagnosed 6 months earlier. The rash advanced proximally and developed a bluish discoloration with petechia. Within 72 hours, eschars developed between the third and the fourth toes and also between the fourth and fifth toes (Fig 1). Radiographs of the left foot showed no evidence

of bone infection, but septate hyphae were seen in a potassium hydroxide (KOH) preparation, and multiple specimens taken between the fourth and fifth toes yielded *Fusarium* infection. A state reference laboratory later made a definitive diagnosis of *F solani*.

On day 18 of hospitalization (neutropenia day 15), multiple eschars with a thin rim of erythema developed on the patient's scalp and abdomen. A nontender subcutaneous erythematous nodule appeared on his right inner canthus. The dosage of itraconazole was increased from 200 to 400 mg b.i.d., and measures were taken to obtain experimental voriconazole for compassionate use. Because the patient's creatinine had risen to 1.9 mg/dL, ABLC was replaced with liposomal amphotericin B at 7.5 mg/kg per day. Soon thereafter,

granulocyte colony-stimulating factor (G-CSF) was administered and the dosage was increased to 10 mg/kg per day. Although the serum creatinine levels stabilized at 1.8 mg/dL while on amphotericin B, his foot lesions progressed, accompanied by new eschars on the scalp. The patient also began to complain of intermittent diplopia and blurred vision.

Intravenous voriconazole (300 mg b.i.d.) was instituted 3 weeks after admission. After 2 days, pedal edema and erythema had subsided. On day 25, the patient's WBC count recovered and the absolute neutrophil count (ANC) exceeded $500 \times 10^9/L$. In the subsequent days, the toe ulcers began a slow resolution with new granulation tissue. No new cutaneous lesions were noted, and old ones began to recede in both size and erythema.



Fig 1. — *Fusarium solani* eschars between the toes of a patient with acute myelogenous leukemia.

Magnetic resonance imaging (MRI) and a CT scan revealed an elliptical-shaped left cerebellar focus (3.5 × 2 cm) of low attenuation consistent with a hematogenously disseminated *Fusarium* lesion (Fig 2). After voriconazole was begun, the visual changes resolved within 2 days. The patient continued to receive intravenous voriconazole for the remainder of the hospital course with continued improvement of all abnormalities. Following discharge, he completed an additional 8 weeks of oral voriconazole. During that period, the skin lesions resolved completely. The cerebellar focus also responded, shrinking in size by approximately two thirds and becoming less attenuated.

Six months after discharge, the patient's leukemia again relapsed, and induction chemotherapy was renewed. Initially, itraconazole prophylaxis was followed by ABLC (5 mg/kg per day), but when neutropenia reappeared, coverage was switched to 200 mg of intravenous voriconazole given twice daily. Despite several weeks of neutropenia, no evidence of recurrent infection was seen. Thus, during this period, voriconazole alone provided effective prophylaxis against this fungal infection. Two weeks after recovering the white blood cell counts, however, the patient died of ischemic colitis and sepsis syndrome but with no evidence of recurrent *Fusarium* infection.

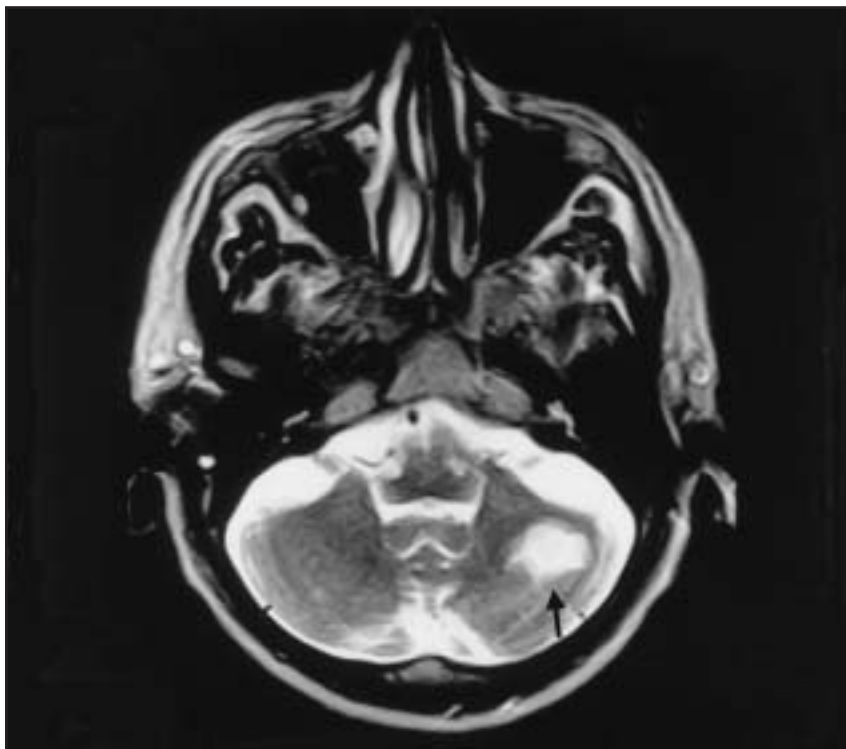


Fig 2. — MRI shows a left cerebellar focus of *Fusarium solani* in a patient with acute myelogenous leukemia (arrow).

Discussion

As illustrated by our case, the most common initial presentation of a disseminated *Fusarium* infection in the neutropenic patient is a persistent fever refractory to antibiotics.¹⁰ Sinusitis, pneumonia, or cutaneous lesions may ensue. In an extensive review of patients with hematologic malignancies, the portal of entry was the skin in 33% of patients, sinopulmonary tree in 30%, and unknown sites in 37%.¹⁰ Skin involvement is typical. In a literature review supplemented by 45 new cases from Brazil, Nucci and Anaissie² reported cutaneous involvement in 72% of immunocompromised patients. Likewise, 8 (72.7%) of 11 immunocompromised patients in Saudi Arabia yielded cutaneous *Fusarium* isolates.⁵ The initial finding of paronychia with pedal foot cellulitis suggests that the infection in our patient had a cutaneous entry.^{2,10} Our patient also had a variety of cutaneous forms that coexist in metastatic fusariosis: macules, papules, pustules, and nodules.¹ The most frequent skin lesions among patients with disseminated disease are multiple, painful, erythematous papular or nodular lesions, with or without later central necrosis.^{2,19} The “target” lesion, described as an ecthyma gangrenosum-like lesion that may be surrounded by a zone of erythema, is thought to be pathognomonic to fusariosis.²⁰ That finding is supported by our case.

While dissemination may involve any organ, those most frequently involved are the sinuses,

lung, and skin. Less often encountered are brain abscesses, endophthalmitis, cystitis, endocarditis, osteomyelitis, septic arthritis, and peritonitis. Relatively few cases of cerebral or meningeal fusariosis have been documented, and patients with these complications have typically succumbed to their infections.²⁰⁻²⁴ We suspected brain involvement after our patient developed bilateral diplopia with vertigo and confusion. A lesion in the left cerebellar hemisphere was discovered on CT scan and confirmed by MRI.

Although we did not document angioinvasion or fungemia, metastatic skin lesions are associated with fungemia.² Attempts to isolate *Fusarium* from the blood of immunocompromised patients are often successful.^{2,10,19,25}

For more than three decades, amphotericin B has been the mainstay for treatment of serious fungal infections, but therapy for fusariosis has remained inadequate. Current antifungals are limited by multiple toxicities and a well-documented resistance. Pujol et al²⁶ studied the in vitro antifungal susceptibility of 11 *Fusarium* isolates including those usually responsible for infection: *F solani*, *F oxysporum*, and *F verticillioides*. These isolates were resistant to amphotericin B, itraconazole, fluconazole, ketoconazole, miconazole, and flucytosine.

In a randomized, multicenter comparison of empirical treatment in patients with neutropenia and persistent fever, voriconazole was

as effective as the gold standard, liposomal amphotericin B, and was superior in reducing documented breakthrough infections, infusion-related toxicity, and nephrotoxicity.²⁷ In another randomized clinical trial of voriconazole, Herbrecht et al²⁸ demonstrated the first significant advance over the standard amphotericin B in invasive aspergillosis. Initial therapy with voriconazole led to better responses, improved survival, and fewer severe side effects. In acute invasive aspergillosis, voriconazole was more effective in pulmonary or tracheobronchial involvement (60% of cases achieved good responses) than in skin invasion (16%), and it was also better in patients with hematologic disorders (58%) than in those with allogeneic stem cell transplants (23%).²⁹ Side effects include visual hallucination and episodes of confusion, but these symptoms usually do not cause the drug to be discontinued.²⁸

Mortality rates from disseminated *Fusarium* infection for patients who receive conventional therapy may approach 80%.⁷ The condition of our patient deteriorated steadily despite stable renal function while he received high-dose amphotericin B. Neutropenic fevers continued and his foot cellulitis spread proximally until amputation became a consideration. Fortunately, we were able to obtain a prompt clinical response from the compassionate use of voriconazole. The cellulitis began to regress within 2 days of instituting therapy, thus saving his foot, and metastatic cutaneous lesions ceased to appear.

Voriconazole is a second-generation antifungal triazole that inhibits cell wall synthesis and represents a broadening of the activity of fluconazole. It has been approved by the Food and Drug Administration for primary treatment of aspergillosis and for refractory infection with *Scedosporium apiospermum* (the asexual form of *Pseudallescheria boydii*) and for *Fusarium* sp. It will likely become the treatment of choice for serious infections with those filamentous fungi. Voriconazole is marketed for intravenous and oral administration. Being lipophilic, the compound achieves high levels in the central nervous system, nearly 2-fold that in the serum³⁰⁻³³ In a successful treatment of probable aspergillosis, high levels were noted in the serum and CSF, with a trend toward accumulation.³⁴ Surgical drainage and long-term use of intravenous voriconazole led to resolution of a frontoparietal abscess documented as *P boydii* by histology and culture.³⁵ It is not yet known if resistance appears during treatment. Drugs that are contraindicated during voriconazole use include long-lasting barbiturates (phenobarbital) and other drugs that accelerate voriconazole metabolism (rifampin, rifabutin, and carbamazepine).³¹ There is no evidence to support the use of voriconazole in zygomycoses.³⁶

In our patient, the therapeutic responsiveness of the intracerebral lesion was confounded by the simultaneous recovery of the patient's neutropenia. As is often the case in disseminated infection with brain lesions, we can only

assume that peripheral and central lesions share a common etiology. Most patients with *Fusarium* infection and hematologic malignancies fail to respond to antifungal therapy until their neutropenia has subsided and remission of the underlying malignancy has occurred.^{1,10} Two days prior to voriconazole therapy, our patient received G-CSF, and his WBC count increased from $0.08 \times 10^9/L$ with an ANC of $0.54 \times 10^9/L$. A bone marrow biopsy at that time also revealed remission of his AML. However, Austen et al²⁵ cautioned that even recovery from neutropenia and good initial response to amphotericin may not prevent a relapse of disseminated *F dimerum* infection.

A high index of suspicion towards recurrent infection is justified by a protracted neutropenic fever that is unresponsive to antibiotics, amphotericin B, or its lipid formulations. Because *Fusarium* infections may have multiple ports of entry, symptoms of sinusitis and pneumonias should undergo thorough evaluation, perhaps even including surveillance cultures. Likewise, judicious examination of the skin including the periungual toes and their web spaces, should rule out fusariosis before contemplating immunosuppressive therapy.² Suspicious lesions should undergo biopsy and culture for early diagnosis and targeted for aggressive antifungal therapy. *Fusarium* infections may mimic aspergillosis¹⁰ but they are less responsive to therapy with amphotericin B. A decision to prolong myelosuppressive chemotherapy must be weighed against the con-

siderable danger of disseminated *Fusarium* infections and their marked tendency to recur from occult foci.²⁵ Patients with leukemia or lymphoma who take maintenance chemotherapy and who develop repeat episodes of neutropenia are at high risk of fatal disseminated disease, including life-threatening CNS infection. Amphotericin B and itraconazole are of limited value in such cases,¹⁰ but voriconazole may provide life-saving therapy.

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