

Treatment of Zygomycosis With Posaconazole in a Patient With Acute Myeloid Leukemia

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The incidence of systemic fungal infection caused by pathogenic and opportunistic organisms is increasing.¹⁻⁴ This increase may be explained in part by the growing number of people with compromised immune function as a consequence of intensive cancer chemotherapy, use of immunosuppressants for organ transplantation, and acquired immune deficiency syndrome.² Zygomycosis (mucormycosis) is the second most common mycosis, after aspergillosis, caused by filamentous fungi.⁵ Although it is observed most often in neutropenic patients with hematologic disease, it also is a major complication of other chronic debilitating diseases, such as uncontrolled diabetes mellitus.^{1,5} Species of *Rhizopus*, a filamentous mold found in soil, decaying food, and animal feces, account for most cases of zygomycosis.⁶

Rhino-orbital-cerebral zygomycosis is the most common type of zygomycosis, occurring in approximately 44% of patients.⁶ Disease outcomes are often negative.⁷ Disease management is multimodal and includes correction of the underlying immunosuppression (eg, reversal of neutropenia and control of glucose levels in patients with diabetes mellitus), aggressive surgical debridement of the infected tissue (if possible), and prompt high-dose antifungal therapy.⁷⁻⁹ Nevertheless, the mortality rate among patients with rhino-orbital-cerebral zygomycosis is approximately 40–50%, and survivors typically have significant morbidity.⁹

The need for new antifungal agents is warranted by limitations of current antifungal therapy coupled with the changing spectrum of fungal disease over the past 2 decades. Posaconazole (Schering-Plough Corporation) is a new extended-spectrum triazole with activity against

a wide range of fungal pathogens being investigated in phase III clinical trials for the prophylaxis and treatment of refractory invasive fungal infection. A recent report from Dannaoui et al¹⁰ showed that posaconazole has in vitro activity against *Rhizopus* species at 24 hours (minimum inhibitory concentration for 90% of isolates [MIC₉₀], 0.5 mg/L), which is better than that of amphotericin (MIC₉₀, 1 mg/L), itraconazole (MIC₉₀, 4 mg/L), and voriconazole (MIC₉₀, 64 mg/L). Although amphotericin B has been considered the standard of therapy for patients with zygomycosis, these data indicate that posaconazole therapy should be studied for the treatment of this disease.

The following is a case of rhino-orbital-cerebral zygomycosis in a patient with acute myeloid leukemia (AML) in whom posaconazole was effective in arresting the refractory fungal infection.

Case Report

In late May 2000, a 51-year-old man was admitted to a community hospital for induction chemotherapy for AML (French-American-British classification M1) with cytarabine 334 mg daily, given via continuous intravenous (IV) infusion for 7 days, and idarubicin 20 mg daily, administered as an IV push for 3 days. In mid-June, right-eye proptosis developed and initially was diagnosed as bacterial sinusitis based on isolation of *Enterobacter aerogenes* and *Stenotrophomonas maltophilia* from the sinus cultures. The patient was given fluconazole and broad-spectrum antibiotics, including piperacillin-tazobactam and vancomycin, as part of febrile neutropenia precautions. A biopsy of the ethmoid tissue revealed broad aseptate ribbon-like fungal hyphae morphologically consistent with *Mucor* species. Associated vascular invasion and thrombosis were noted. An orbital biopsy and ethmoidectomy was performed the following day, revealing broad, irregularly shaped hyphae with right-angle branching and

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without septae in the vessel lumina, in vessel walls, and within markedly inflamed and necrotic tissues, which was morphologically consistent with Mucorales. However, no fungal elements were evident in the bone fragments of the orbit. Fungal cultures from the right middle turbinate at this time were positive for *Rhizopus* species; however, they were not sent for susceptibility testing. Corresponding computed tomographic (CT) examination of the head showed right maxillary sinusitis with aggressive invasive features involving the right orbital apex and extending to the optic canal. Obliteration of fat planes, rather than frank bone destruction, is the earliest sign of invasive sinus disease; therefore, the listed imaging findings led to the diagnosis of rhino-orbital-cerebral zygomycosis.¹¹ As a result of this disease process, the patient completely lost sight in the right eye. Conventional amphotericin B therapy at a dose of 1 mg/kg was started at this time. After a prolonged period of aplasia (at least 30 days), a repeat bone marrow biopsy was performed in late June that revealed marrow composed of at least 50% residual leukemia, thus rendering the patient functionally neutropenic. Despite the ongoing invasive fungal infection, the patient started reinduction therapy 10 days later, with cytarabine 2,000 mg/m² (dose = 3,200 mg), given IV every 12 hours for a total of 8 doses, plus mitoxantrone 12 mg/m² per day (dose = 20 mg) for 3 days. The patient remained pancytopenic for an additional 3 weeks. After approximately 2 weeks of conventional amphotericin B therapy, the left eye became inflamed, which resulted in concern for fungal spread; however, this resolved on hematologic recovery.

Despite hematologic recovery, complete remission of his underlying AML, and 61 days of amphotericin B deoxycholate therapy (total dose = 3,471 mg), repeated CT scans of the head showed clear spread of zygomycosis with destruction of the walls of the right maxillary sinus, including the floor of the right orbit, and with possible intracranial extension. The patient declined further surgical maneuvers or enucleation at this time.

In late August, approximately 2 months after external ethmoidectomy and debridement, the patient was transferred to Shands Hospital at the University of Florida for enucleation and follow-up, as well as for consideration for hematopoietic stem cell transplantation (HSCT). Intravenous amphotericin B lipid complex (ABLCL) therapy at a dose of 5 mg/kg per day was initiated, and conventional amphotericin B therapy was discontinued. A CT scan obtained at this time showed worsening infection, with involvement of the entire retro-antral fat pad and pterygopalatine fossa, as well as orbital apex, with spread into the optic canal (Figure 1). Zygomycosis also had spread from the orbital apex to the superior orbital fissure, ending at the anterior edge of the cavernous sinus and within

1–2 mm of the anterior aspect of the cavernous segment of the carotid artery, to the central skull base surrounding the foramen rotundum, and to the greater wing of the sphenoid bone. The base of the pterygoid plates and related central skull base were destroyed through involvement of the sphenoid sinus floor.

The patient underwent enucleation of the right orbit with sphenoidectomy. Debris consistent with fungal elements was identified in the ethmoid sinuses and within the orbit. Fungal invasion of the optic nerve was evident as it entered the anterior cranial fossa. Fungal infection was not evident in the sphenoid sinus. Fungal stains from the right ethmoid contents again revealed zygomycosis. The ABLCL dose was increased to 7.5 mg/kg per day on the second day of hospitalization. Despite 12 days of high-dose ABLCL, a follow-up CT scan 6 days after enucleation showed soft-tissue extension of the disease into the upper infratemporal fossa and the right frontal lobe. By this time, the patient had received a total of 3,471 mg of conventional amphotericin B and 4,800 mg of ABLCL.

Because the patient's condition did not respond to amphotericin B therapy, oral posaconazole 200 mg 4 times a day was initiated in early September. After 6 days of oral posaconazole therapy, a CT scan of the head revealed decreasing edema and stable disease. The patient was discharged from the hospital on day 8 of posaconazole therapy, but continued treatment at 400 mg orally twice daily. Serial head CT scans (days 7 and 15 of posaconazole therapy) initially showed stable disease (Figure 2); during the next 2 weeks, edema along the right frontal lobe resolved. On day 33 of posaconazole therapy the patient underwent consolidation chemotherapy with idarubicin 20 mg daily for 2 doses, plus cytarabine 160 mg daily, given via continuous IV infusion for 5 days.

Over the next 4 months, posaconazole maintained stable to slightly reduced disease (Figure 3), enabling the patient to undergo nonmyeloablative HSCT. Repeated CT scans on days 41, 47, 67, 83, 100, 112, 135, 146, 153, 183, and 190 of posaconazole therapy demonstrated stable to mildly improved disease. Posaconazole therapy was continued throughout the posttransplantation course, which was complicated by neutropenic fever and 5 days of pancytopenia. Four granulocyte transfusions were administered when the patient was neutropenic to minimize reactivation of the zygomycosis. The patient subsequently was discharged on posaconazole therapy and was monitored in the outpatient clinic. Unfortunately, the patient's AML relapsed approximately 33 days after nonmyeloablative HSCT. He showed no evidence of recurrence or progression of fungal disease (with stable changes as assessed by CT scan) until the time of his death, which was attributed to relapsed leukemia. No autopsy was performed. Posaconazole was well tolerated throughout

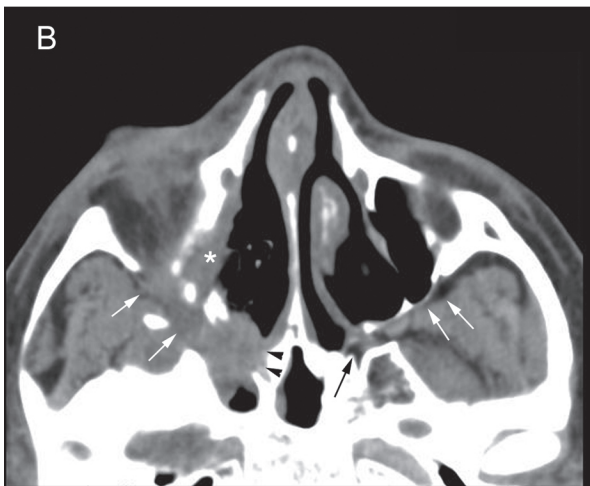
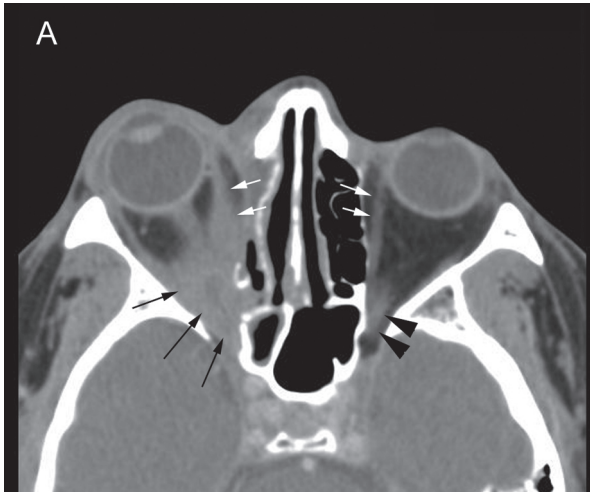


Figure 1. High-resolution axial computed tomographic (CT) images obtained without contrast through the maxillofacial area after 33 days of amphotericin B therapy.

A) The CT image through the orbital apex demonstrates obliteration of the orbital fat planes (black arrows) in the posterior half of the orbit on the right when compared with the left. The optic nerve can no longer be distinguished as a separate structure (black arrowheads on the left point to the normal appearance of the optic nerve at the orbital apex). All these changes are consistent with invasive fungal infection involving the entire orbital apex. Note also the significant thickening of the medial rectus muscle on the right (white arrows on the right) in comparison with the uninvolved side (white arrows on the left), indicating muscular involvement.

B) CT image at the level of the maxillary sinuses shows significant obliteration of the retro-antral fat pad on the right (white arrows on the right) compared with the normal appearance on the left (white arrows on the left), indicative of invasive fungal disease. Infection also extends into the pterygopalatine fossa, reflected as widening and complete obscuration of the fat pad (black arrowheads) within the right pterygopalatine fossa—see its normal appearance on the left (black arrow). Note the mucoperiosteal thickening within the superior aspect of the maxillary sinus on the right (*), the source of the patient's invasive fungal disease.

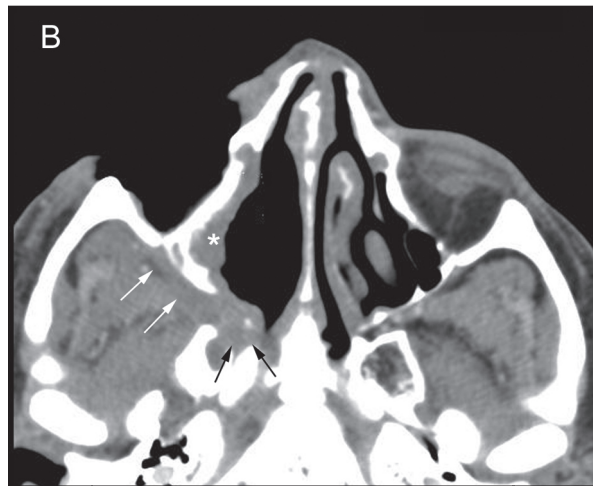
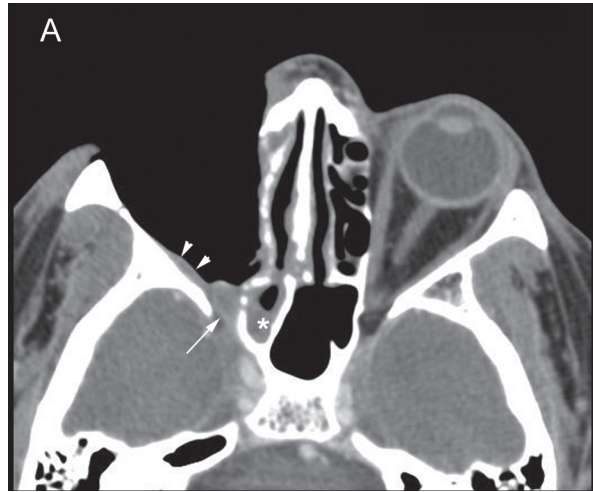


Figure 2. Repeated noncontrast axial computed tomographic (CT) images obtained after enucleation of the right orbit and extensive sinus surgery, and after 6 days of posaconazole therapy.

A) The CT image obtained at the same level as in Figure 1A demonstrates expected changes of surgical enucleation on the right. Only a small soft-tissue lesion is seen at the orbital apex (arrows), and minimal thickening is seen along the lateral orbital wall (arrowheads). These findings are inconclusive and could represent post-surgical changes or persistent invasive fungal disease. A small air fluid level is seen in the sphenoid sinus on the right (*).

B) The CT image at the same level as Figure 1B documents stable obliteration of the retro-antral fat pad (white arrows), indicative of persistent invasive fungal disease with unchanged involvement of the pterygopalatine fossa (black arrows). Mucoperiosteal thickening is also unchanged in the superior aspect of the maxillary sinus (*).

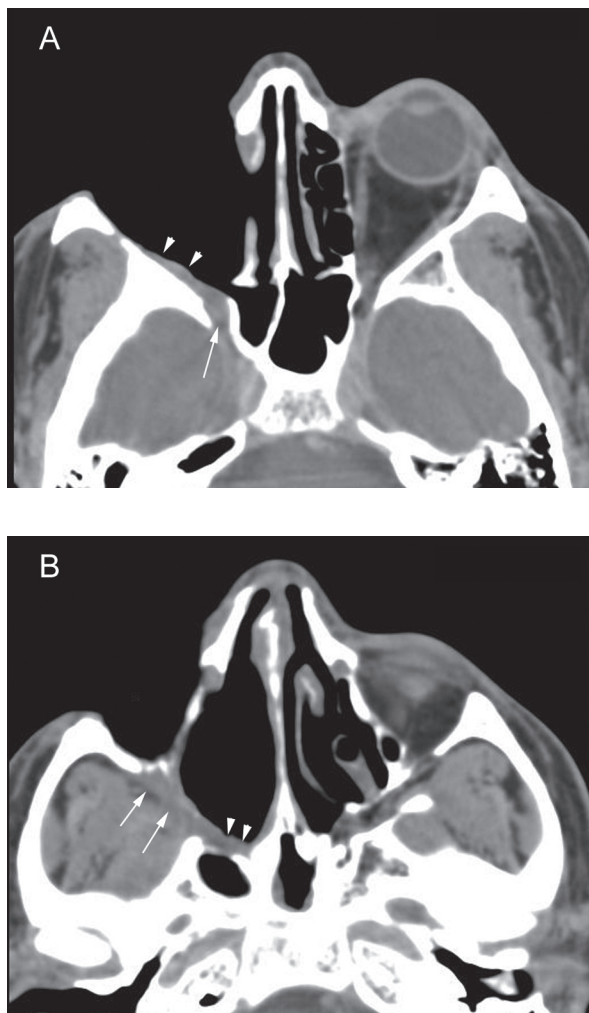


Figure 3. Follow-up non-contrasted axial computed tomographic (CT) images of the affected area obtained after 117 days of posaconazole therapy document significant improvement.

A) CT image obtained at the same level as in Figures 1A and 2A shows unchanged soft-tissue lesion at the orbital apex (arrows) and mucosal thickening along the lateral orbital wall (arrowheads). The sphenoid sinus on the right is now free of disease.

B) CT image at the same level as Figures 1B and 2B demonstrates improvement in the obliteration of the retro-antral fat pad (arrows) and a significant decrease in the previously seen widening of the pterygopalatine fossa, with persistent obliteration of the fat pad in this location (arrowheads). Note also the complete resolution of the mucoperiosteal thickening within the right maxillary sinus.

the duration of treatment, with no adverse events reported. Pharmacokinetic monitoring of posaconazole was not performed.

Discussion

We describe a case of rhino-orbital-cerebral zygomycosis that progressed despite surgical resection and high-dose therapy with 2 formulations of IV amphotericin B. Although surgical resection of the infected tissues combined with a large total dose of amphotericin B likely contributed to the good response observed in this patient, it is notable that a partial response to infection progressive to high-dose polyene therapy was observed after only 1 week of oral posaconazole therapy. While taking posaconazole, the patient could be discharged on therapy without the need for home infusion service. It is important to note that the patient was able to receive further antineoplastic therapy for his underlying leukemia because the fungal infection had stabilized and the cerebral edema had decreased. As salvage therapy, oral posaconazole was a sound choice for 2 reasons. First, in vitro susceptibility tests have shown it to be a more active antifungal agent than both voriconazole and amphotericin B.^{10,12,13} Second, posaconazole was well tolerated in several phase II and III trials involving immunocompromised patients.^{14,15}

In conclusion, posaconazole proved to be an effective and well-tolerated treatment for rhino-orbital-cerebral zygomycosis in this immunocompromised patient and was effective in preventing further spread of the infection. In light of the limited treatment options for zygomycosis, the results of this case suggest that posaconazole may be an appropriate treatment for patients with rhino-orbital-cerebral zygomycosis and that it deserves further study.

Acknowledgments

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Review

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Zygomycosis (mucormycosis, phycomycosis) is an infection caused by the fungi of the orders Mucorales and Entomophthorales. These organisms are ubiquitous and generally saprophytic, rarely causing disease in immunocompetent hosts, but are the third most frequent cause of invasive fungal infection in immunocompromised patients.^{1,2}

The case described by Leather and colleagues is of a classic rhinocerebral zygomycosis diagnosed in a man undergoing induction chemotherapy for AML. Despite early diagnosis and surgical debridement along with treatment with liposomal amphotericin B the infection progressed. Treatment with posaconazole, a new triazole antifungal, along with aggressive surgical debridement, halted disease progression within 1 week of initiation of therapy. After 4 months of oral posaconazole therapy the patient was able to receive an HSCT. Prevention of recurrence after the HSCT was accomplished using posaconazole as secondary prophylaxis.

The agents of zygomycosis are commonly found in the environment on fruit, bread, and soil. The organisms

are common components of decaying organic debris. The most common agent of zygomycosis is *Rhizopus arrhizus*. The infection zygomycosis produced by these species is acute and rapidly fatal despite early diagnosis and treatment.^{1,3} These organisms have a predilection to invade major blood vessels with ensuing ischemia, necrosis, and infarction of adjacent tissues and, thus, production of black pus.

There are 5 major clinical forms of zygomycosis: (1) rhinocerebral, (2) pulmonary, (3) abdominal-pelvic and gastric (gastrointestinal), (4) cutaneous, and (5) disseminated.³

Rhinocerebral zygomycosis is the most frequently encountered form of infection and tends to involve the nasal mucosa, followed by the eye, with extension into the brain. Manifestations may include fever, unilateral facial pain, headaches, nasal congestion, epistaxis, visual disturbances, lethargy, proptosis, and loss of extraocular muscle movement, frequently accompanied by cranial nerve palsy of the II, III, IV, and VI nerves. In addition, black necrotic lesions are generally seen on the hard palate or nasal mucosa of these extremely ill patients.

Primary pulmonary zygomycosis tends to occur in patients with profound neutropenia and those who have been on steroid therapy. The manifestations include fever, a productive cough with hemoptysis, chest pain, and shortness of breath.

Gastrointestinal zygomycosis usually results from ingestion of the organism by either malnourished or renal-failure patients, and produces necrotic ulcerations with ischemia and gangrene of stomach and colon.

Cutaneous zygomycosis may be either primary or secondary. Primary infection is usually due to the direct inoculation of the organism into disrupted integument, and has been associated with use of elastoplast bandages over biopsy sites or in burn patients with prior colonization. Secondary cutaneous infection is seen with disseminated zygomycosis as a consequence of hematogenous seeding.

Disseminated zygomycosis is seen in patients with hematologic malignancies during neutropenia, and begins in the lungs and spreads to the central nervous system producing infarction, necrosis, and abscess formation. It also disseminates to the liver, spleen, kidney, heart, and skin. The infection generally begins with the inhalation of conidia into the respiratory tract, and subsequently spreads hematogenously throughout the body including the central nervous system.

Differential diagnosis includes infections due to *Aspergillus* species, *Scedosporium apiospermum*, and other filamentous molds.

Unfortunately, the laboratory studies are nonspecific and the diagnosis relies upon a high index of suspicion, in a host with appropriate risk factors and evidence of tis-

sue invasion.³ There are no serologic tests available, and the blood cultures are of no benefit. Fungal culture of biopsy tissue may be helpful, but is frequently negative despite positive histopathology. Fungal cultures are only positive in about 15–25% of cases. On histopathology, fixed tissue can be stained with hematoxylin and eosin and may demonstrate fungal hyphae using the Grocott silver methenamine stain or periodic acid-Schiff stain. The classic appearance demonstrates the fungus as broad, nonseptate hyphae with acute angle branching. Imaging studies may provide additional information and assist with the diagnosis.

Successful treatment of zygomycosis requires a high index of clinical suspicion for an early diagnosis.^{3,4} Treatment requires: (1) reversal of underlying condition, (2) wide and extensive surgical removal of the affected tissue, and (3) early antifungal therapy. Since the fungus is relatively resistant to amphotericin B, current therapy consist of lipid formulations of amphotericin B (ABL CET or Ambisome, Gilead) at a minimum dose of 5 mg/kg per day, occasionally using doses of 8–15 mg/kg per day.³ Using this aggressive therapeutic approach, several authors have demonstrated slightly improved outcome in their patients with rhinocerebral zygomycosis, the most fulminant form of the disease.

Posaconazole is a novel synthetic lipophilic triazole antifungal, structurally similar to itraconazole.³ It is currently in late phase III clinical development and has demonstrated excellent in-vitro activity against many yeast and molds, including many of the Zygomycetes.⁵ It is orally absorbed and extensively distributed into tissues. The preclinical data suggest that posaconazole may be a rational choice for the treatment of infections due to the Zygomycetes.⁶ In an open-labeled clinical trial using posaconazole in patients (N=24) who were either antifungal refractory or intolerant of conventional antifungal therapy, posaconazole demonstrated an overall response rate of approximately 66%.⁷

In addition to the antifungals, there are several reports demonstrating a successful outcome in patients given combination therapy with amphotericin B and granulocyte-macrophage colony-stimulating factor.⁸

The clinical response seen in this patient along with the clinical responses observed in the open-labeled clinical trial suggest that posaconazole may be an effective treatment alternative for zygomycosis.

In spite of the newer antifungals, however, the overall prognosis of the infection depends on several factors including site of infection, rapidity of diagnosis, and type and severity of immunosuppression. The mortality rate is still approximately 60–85% for patients with the rhinocerebral form of infection, and the overall mortality rate is approximately 50%.

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