# Mucormycosis (Zygomycosis) in a Heart-Kidney Transplant Recipient: Recovery after Posaconazole Therapy

**Angela Ma Tobón,[1] Myrtha Arango,[1,2] Darío Fernández,[3] and Angela Restrepo[1]**

[1]Corporación para Investigaciones Biológicas, [2]Facultad de Medicina, Universidad de Antioquia, and [3]Clínica Cardiovascular Colombiana, Medellín, Colombia

**We describe the case of a diabetic patient who developed a severe invasive fungal infection due to *Rhizopus* species postoperatively after a dual heart/kidney transplantation with subsequent intensive immunosuppressive therapy. No improvement was noted with amphotericin B (deoxycholate) therapy, but salvage treatment with the new azole antifungal posaconazole (200 mg orally 4 times daily) resulted in dramatic clinical improvement as early as 1 week after the initiation of therapy that continued through 23 weeks of treatment, with marked clinical, mycological, and radiological improvements and no adverse events.**

Mucormycosis (zygomycosis) refers to fungal infection caused by Zygomycetes belonging to the order Mucorales (e.g., *Absidia, Mucor,* and *Rhizopus* species). These organisms are characterized by broad, aseptate hyphae and rapid growth. Because Zygomycetes are found in soil, air, and decaying matter, human contact with spores is common [1–3], although infections typically occur in immunocompromised and diabetic individuals [1–5]. Most infections are acquired by inhalation; traumatic implantation and ingestion also are portals of entry [1, 2, 4, 6, 7]. Mucormycosis is usually acute and progressive, with mortality rates in the range of 70%–100% [1–4, 8]. Zygomycetes have a marked predilection for blood vessels and produce multiple emboli, resulting in necrosis of the surrounding tissues [1, 2, 4, 9]. The treatment of mucormycosis is multifactorial and consists of a combination of high-dose amphotericin B, surgical resection, and control of predisposing conditions [1, 2, 10–12]. The nephrotoxicity of amphotericin B limits its use in patients with renal disease [10, 13, 14], leaving patients with drug intolerance with no alternatives. We describe the outcome of a patient who developed mucormycosis of the skin and heart after organ transplantation that was successfully treated with the new triazole derivative, posaconazole.

***Case report.*** In January 1999, a 56-year-old male city dweller with fibrocystic kidney disease began ambulatory hemodialysis after he developed chronic renal insufficiency due to interstitial nephritis. Pretreatment diagnoses included arterial hypertension, severe dilated cardiomyopathy, type 1 diabetes, and hypercholesterolemia. In November 2000, the patient underwent dual (heart and kidney) transplantation. In early December, the thoracic surgical wound was erythematous with purulent drainage; *Pseudomonas* species were cultured, and antibacterial therapy was initiated. The wound infection progressed to involve the subcutaneous tissues and surrounding muscle, resulting in wound dehiscence. During wound incision and debridement, necrotizing fasciitis was observed. Surgical specimens of the wound material showed fragments consistent with fungal hyphae. However, these cultures grew *Klebsiella* species, which complicated the identification of the fungal organism and delayed the administration of appropriate treatment. A new course of antibiotic therapy was initiated, but the patient showed no improvement. Approximately 5 days later, the patient had a fever (temperature, 40°C) and chills, despite receiving antibacterial therapy.

One week after the operation, an MRI showed cardiomegaly and loculated pleural and pericardial effusions (figure 1). The transplanted kidney appeared to be healthy, and there was no intra-abdominal fluid collection. Amphotericin B deoxycholate therapy (1 mg/kg q.d.) was initiated under a presumptive diagnosis of aspergillosis. In January 2001, MRI findings prompted another thoracic operation, which showed nonpurulent mediastinitis; a dry, gray mass adherent to the pericardium; and accumulation of a brown liquid. Samples from the mass and the external wound showed aseptate filaments with right-angle branching suggestive of a Zygomycete; corresponding cultures grew *Rhizopus* species. Antifungal susceptibility testing showed MICs of 0.5 μg/mL for amphotericin B, 8 μg/mL for itraconazole, >64 μg/mL for fluconazole, and 4 μg/mL for posaconazole [15].

Despite appropriate aggressive surgical intervention and ongoing antifungal therapy, the patient's condition deteriorated. He was unconscious and hemodynamically unstable, and his

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Reprints or correspondence: Angela Restrepo, Corporación para Investigaciones Biológicas, Carrera 72A, 78B-141 Medellín, Colombia (angelares@geo.net.co).

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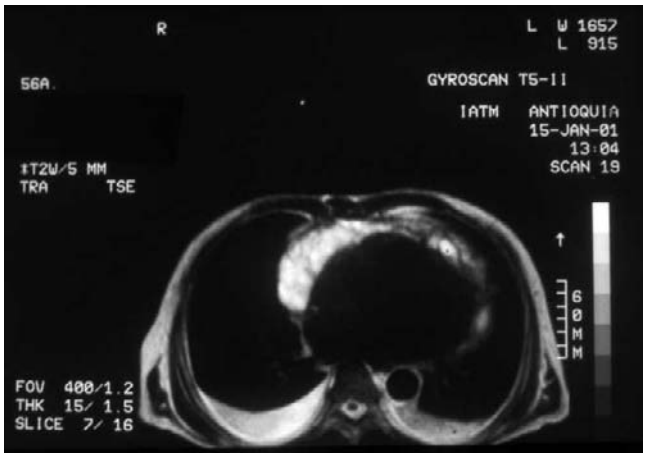


**Figure 1.** MRI obtained before therapy. Bilateral pleural and pericardial fluid accumulation with honeycombed partitions are present.

blood glucose concentration was 250 mg/dL. Two days after the operation, after a cumulative dose of 1600 mg, amphotericin B therapy was discontinued because of transplant deterioration, pathologic pericardial changes, and abnormal increases in blood urea nitrogen (BUN; 50 mg/dL) and serum creatinine (2.5 mg/dL) levels. The patient received amphotericin B for ~6 weeks.

Treatment with oral posaconazole (200 mg q.i.d.) was begun the next day. Concomitant medications included insulin, cyclosporine (75 mg b.i.d.), prednisolone (5 mg q.d.), ganciclovir, ranitidine, magnesium, trimethoprim-sulfamethoxazole, acetaminophen, salicylates, enalapril, and low-molecular-weight heparin.

After 7 days of posaconazole treatment, the patient regained consciousness and no longer exhibited altered neurological function but remained febrile (temperature, 38.5°C). Serum creatinine and BUN levels decreased to 1.90 and 32 mg/dL, respectively; his blood glucose level was 120 mg/dL. After 2 weeks of posaconazole therapy, the patient's fever had resolved, and he was hemodynamically stable but weak, without neurological abnormality. The surgical incision was clean but had not yet healed. Posaconazole was well tolerated, with no adverse effects. An echocardiogram done in February 2001 showed pericardial fluid collection, and an MRI revealed a thickened (2 mm) pericardium and honeycombed fluid accumulations over the right pleural and pericardial cavities. There was no sign of constriction, although bilateral pleural effusions were still present.

After 3 weeks of oral posaconazole treatment (~4 weeks after the operation), the patient's condition was satisfactory; he was afebrile and ambulatory, and the surgical wound was nearly completely healed. Azathioprine (25 mg q.d.) was added to the immunosuppressive regimen. By treatment week 4, the patient was discharged from the hospital.

The findings of a follow-up echocardiogram at treatment week 5 were normal. In March 2001, after 6 weeks of treatment with posaconazole, culture of a cardiac biopsy sample obtained through catheterization was negative for fungus. The prednisolone and azathioprine dosages were increased to 10 and 50 mg per day, respectively.

By the end of treatment week 11, the patient was asymptomatic, and, by treatment week 18 (May 2001), he had returned to work. His immunosuppressive regimen was reduced to cyclosporine (100 mg q.d.) and prednisolone (10 mg q.d.). Pleural and pericardial effusions were no longer evident on MRI; the remaining minor pericardial thickness of the right anterior and lateral pericardial areas was indicative of scarring (figure 2). The heart chambers were normal.

The patient continued posaconazole therapy (400 mg b.i.d.) through June 2001, completing the planned 23 weeks of continuous treatment. He had no major adverse effects and continues to be healthy.

***Discussion.*** Mucormycosis is serious and life threatening. Dissemination of the fungus from the site of primary infection may result in rapid spread to visceral organs [7]. This appears to have occurred in our patient, because the first site of infection was a surgical wound. Pericardial and pleural involvement followed, which resulted in significant clinical abnormalities of the mediastinal region, including pericardial and pleural effusions and enlargement and malfunction of the transplanted heart. The occurrence of cardiac and pleural mucormycosis has been reported in the literature [1, 2, 16–18]. Although necrotizing and rapidly progressing infection is typical, the course of infection in our patient was protracted, occurring ~7 weeks before dissemination to the cardiac and pleural regions became detectable.

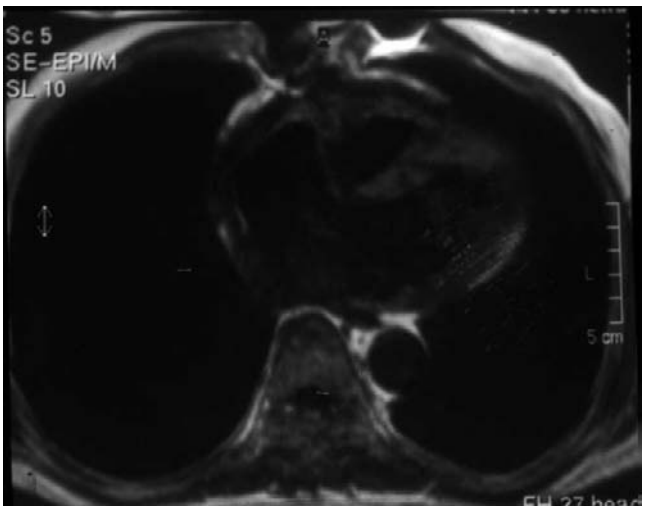


**Figure 2.** MRI obtained after therapy. No pleural effusion is seen, although there is residual thickening of the pericardial anterior wall.

The treatment of mucormycosis includes a combination of antifungal therapy, wound debridement, and management of predisposing conditions [2, 4, 10, 11]. None of the azoles that were previously available (ketoconazole, fluconazole, and itraconazole) are active for the treatment of mucormycosis [1, 2]. Surgical wound debridement alone has enhanced the progression of lesions only hours after surgery [14]. Amphotericin B can be ineffective for patients in whom disease is detected late or who have disseminated disease [1, 2]. This appears to be the case in our patient, in whom skin lesions progressed and infection disseminated to the pericardium during a 6-week course of high-dose amphotericin B treatment. *Rhizopus* species were isolated from both the surgical wound and the pericardial masses, indicative of an active fungal infection. In addition, the patient's condition had deteriorated, and he was severely ill even after receiving a cumulative dose of amphotericin B of 1600 mg.

Posaconazole is a new triazole antifungal with excellent activity in vitro against a broad spectrum of yeasts and hyaline molds, including *Aspergillus* and *Fusarium* species, dematiaceous molds, and other fungi [12, 19]. Posaconazole has shown in vitro activity comparable to that of amphotericin B against *Rhizopus* species, *Mucor* species, and other Zygomycetes [20]. In a study that examined the in vitro susceptibility of 36 isolates of Zygomycetes to posaconazole and other antifungals, posaconazole demonstrated an overall $MIC_{90}$ of 1 $\mu$g/mL, whereas the overall $MIC_{90}$ of voriconazole was 32 $\mu$g/mL [21]. Although the in vivo efficacy of a related azole (SCH42427) in an animal model of pulmonary mucormycosis initially suggested the potential of azoles for management of mucormycoses [22], it is clear that the activity and efficacy of azoles will vary by agent.

In our patient, who had severe postsurgical deterioration during a 6-week course of high-dose amphotericin B therapy, the excellent response to emergency treatment with posaconazole deserves comment. Improvement was seen after 7 days of treatment and continued over time such that, after 10 weeks of taking posaconazole, the patient was asymptomatic, with no fungi detected on routine posttransplant heart biopsy (KOH and culture). This response is remarkable, considering the seriousness of the infection and the risk factors in this patient. In the medical literature, only 1 case of survival (an immunocompetent 22-month-old boy) with mediastinal organ involvement has been reported [3].

The present case exemplifies the potential benefits of treatment with oral posaconazole for patients with mucormycosis. Although a single case report does not permit us to reach definitive conclusions on the effectiveness of this new triazole, it supports the need for the development of an experimental model of mucormycosis in which to further study its usefulness. Zygomycetes have been difficult to culture from specimens of infected tissues in both experimental and patient infections, making an evaluation of efficacy problematic [23]. To date, there have been few studies on only a small number of isolates that have examined the in vivo efficacy of antifungals in animals experimentally infected with Zygomycetes. In a recent study, posaconazole had activity in vivo against 3 isolates of *Mucor* species in a neutropenic mouse model of disseminated infection, significantly reducing tissue burden—in many cases to undetectable levels—and increasing survival [24]. On the basis of the results seen in our case, a recommendation can be made for posaconazole as a well-tolerated and effective salvage treatment for mucormycosis, even in seriously ill patients.

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