Postrenal transplant renopulmonary zygomycosis with vascular aneurysms responded to surgical treatment and salvage therapy with posaconazole after failure to respond to liposomal amphotericin

Zaina Al Maskari¹, Faryal Al Lawatia²

¹ Department of Microbiology, Royal Hospital, Muscat, Sultanate of Oman
² Department of Medicine, Royal Hospital, Muscat, Sultanate of Oman

Summary

Background: Zygomycosis is a difficult to treat and frequently fatal infection affecting immunocompromised and (rarely) immunocompetent patients. It requires a multifaceted approach involving elimination of predisposing factors, surgical debridement, and antifungal therapy.

Case Report: We report the case of a postrenal transplant patient who developed disseminated zygomycosis with vascular aneurysms after receiving empirical voriconazole treatment for presumed pulmonary fungal infection in addition to immunosuppression and methylprednisolone pulses for presumed graft rejection, as renal biopsy was declined. Initially, liposomal amphotericin therapy in combination with surgical intervention failed. Addition of posaconazole as salvage therapy improved the patient outcome. He received total of 6 weeks of AmBisome and 12 weeks of posaconazole.

Conclusions: Zygomycosis is a difficult to treat infection. Management includes surgical debridement and antifungal therapy, namely liposomal amphotericin. However, in cases where treatment with liposomal amphotericin along with surgical intervention fails, posaconazole can be given as a salvage therapy. Duration of antifungal treatment should be determined on an individual basis.

Key words: renopulmonary • zygomycosis • postrenal transplant • posaconazole therapy
BACKGROUND

Zygomycosis is a difficult to treat and frequently fatal infection affecting immunocompromised and (rarely) immunocompetent patients. It requires a multifaceted approach involving elimination of predisposing factors, surgical debridement, and antifungal therapy. Lipid formulation of amphotericin B has been the treatment of choice. The use of posaconazole has been successful in salvage trials but should not be used as first-line therapy until an effective intravenous formulation is available. We report the case of a patient with a history of renal transplant, who developed renopulmonary zygomycosis with vascular aneurysms after voriconazole treatment for presumed pulmonary fungal infections. He was managed with nephrectomy and had multiple surgical debridements along with liposomal amphotericin therapy. However, as the patient did not improve, posaconazole was added as a salvage therapy and he showed clinical and radiological improvement.

CASE REPORT

A 22-year-old Omani male, with a known case of chronic renal failure secondary to Alport syndrome, was admitted to our hospital directly from Pakistan, where he had unrelated donor renal transplant 11 days earlier, with the complaint of fever and cough. He was receiving cyclosporine 175 mg BD, mycophenolate (500 mg BD) and hydrocortisone (100 mg TID for 15 days, then dose was tapered gradually), as well as cotrimoxazole prophylaxis.

On examination he was febrile (38°C); chest and other systems examination revealed no signs of infection. His initial workup showed a white cell count of 9.8×10⁹/L, CRP: 11.9 mg/L, and blood culture was negative. Chest x-ray was normal and kidney ultrasound showed no abnormal findings. On admission he developed hemoptysis and tachypnea. An urgent CT scan of the chest showed patchy density on the left lower lobe (Figure 1) suggestive of pulmonary hemorrhage and he was started empirically on piperacillin – tazobactam. While waiting for his workup for autoimmune diseases results, he was managed with methylprednisolone pulses and plasma exchange at the surgical site. CT abdomen showed right iliocostal, and friable graft with minimal pus. Five days post-procedure, however, fever recurred with abdominal pain and discharge at the surgical site. CT abdomen showed right iliocostal abscess (Figure 2).

The patient underwent wound exploration. Fluid sent from the abdominal collection grew asceptate fungus later identified as Zygomycetes species (further speciation was not done). Histopathology of the excised kidney showed asceptate hyphae seen in the kidney invading blood vessels. He was started on liposomal Amphotericin 7 mg/kg/day. Despite high doses of liposomal Amphotericin for 3 weeks, he remained febrile with persistent leucocytosis. Abdomen and pelvic CT showed 2 multiloculated formations with pseudocystic, and friable graft with minimal pus. Five days post-procedure, however, fever recurred with abdominal pain and discharge at the surgical site. CT abdomen showed right iliac fossa abscess.

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Zygomycosis (mucormycosis) is an increasingly emerging fungal infection. This increase has been particularly evident in hematopoietic stem cell transplant recipients (HSCT), Solid Organ Transplant (SOT) and patients with hemato-
logical malignancies [1,2]. Other underlying diseases for this 
lethal infection are: diabetes mellitus, metabolic acidosis, 
treatment with glucocorticoids, solid organ transplant [2], 
treatment with Deferoxamine, iron overload, AIDS, injec-
tion drug use, trauma and malnutrition.

In a review of 116 solid organ transplant recipients with zy-
gomycosis, most cases occurred in renal transplant recipi-
ents with similar clinical presentation among various types 
of organ transplantation, although patients with liver trans-
plantation had a trend of higher incidence of dissemina-
tion (26.3%) (p=0.07) [3]. Marty et al. was first to describe an increased frequency of 
mucormycosis after voriconazole prophylaxis among recipi-
ents of allogenic HSCT. Subsequently, several retrospective 
series from geographically distinct transplant centers in the 
U.S. suggested an association between prior voriconazole ex-
posure and subsequent development of mucormycosis [4]. In 
contrast, in a large prospective study comparing flucona-
zole and voriconazole for the prevention of invasive fungal 
infestations, Wingard et al. did not find excess numbers of cases 
in the voriconazole-treated group (2 mucor cases in 305 
voriconazole-treated patients and 3 cases in 295 fluconazole-
treated patients). However, the rate of invasive fungal infec-
tions in both study arms was low (10.6% in the fluconazole 
group and 6.6% for the voriconazole group at 6 months).

Hence it is not known if this association reflects a true epi-
demiological link, or rather represents a marker of chang-
ing immunosuppression occurring in parallel with the 
evolution of transplant practices and immunosuppression 
strategies [4]. Zygomycetes are angioinvasive, causing infarction of in-
fected tissues. Histologically, characteristic septate broad 
(5–50 µm) hyphae with propensity for invasion of blood 
vessels are seen. Our patient presented with cough and he-
moptyis; it is likely that he had pulmonary zygomycosis that 
was not diagnosed, although his BAL was cultured for fun-
gal infection as well as cytology, and all results were nega-
tive. Despite the ability of these organisms to invade tissues, 
they are rarely isolated from cultures of blood, urine, cere-
brosplinal fluid, sputum, and paranasal sinuses secre-
tions, bronchoalveolar lavage or swabs from infected areas. 
The recovery of zygomycetes from biopsy material may be 
compromised if the processing of the specimens involves tis-
sue grinding, a procedure that kills the non-septate hyphae 
of these fungi. Combining microscopy and culture will in-
crease the diagnostic yield by 15–20% [5]. Our patient re-
ceived voriconazole for almost 3 weeks, which possibly con-
tributed to dissemination to the grafted kidney and led to 
vascular aneurysms. Additionally, he was pulsed with methyl 
prednisolone empirically for possible graft rejection as 
renal biopsy was declined.

The early diagnosis and immediate initiation of treatment 
with an antifungal agent in combination with surgical inter-
vention has proved critical for the favorable outcome of the 
disease. Amphotericin B deoxycholate has been the drug of 
choice for many years and is usually given at high daily dos-
es, which can result in renal toxicity. Currently, liposomal 
Amphotericin B is frequently used for treatment of zymomy-
cosis in order to deliver a high dose with less nephrotoxicity.

Posaconazole has demonstrated in vitro and in vivo activity 
against Zygomycetes.

Two clinical studies have evaluated the efficacy of 
Posaconazole as salvage therapy for zygomycosis. Van Burik 
et al. reported a 60% response in 91 patients and Sun et al. 
found a 79% response in 24 patients. In addition, reports 
have been published showing successful treatment of pa-
tients with zygomycosis, highlighting posaconazole as prom-
ising treatment of these infections [6].

Our patient improved with surgical intervention and sal-
vage treatment with posaconazole. The optimal duration 
of antifungal treatment for Zygomycosis remains an un-
resolved issue, hence treatment duration should be deter-
mined on an individual basis, but therapy usually contin-
ues for at least 6–8 weeks [7].

CONCLUSIONS

Zygomycosis is an increasingly emerging fungal infection, 
especially in immunocompromised patients. Management in-
cludes surgical debridement and antifungal therapy, name-
ly liposomal amphotericin. However, in cases of failure, 
posaconazole can be given as a salvage therapy.

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