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Case Report

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

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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**

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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 BID, mycophenolate (500 mg BID) 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 $9.8\times1O^9$/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 plasmapheresis for suspected Kartagener syndrome. Ten days after admission, he was still febrile, his CRP came up to 79 mg/L, WCC: 14.7×10^9/L and ESR: 51 mm/hour. At that time all his microbiological cultures were negative, including blood cultures, sputum culture and urine cultures. Bronchoscopy was normal and BAL was negative for bacterial culture and acid-fast bacilli (AFB). Histology was negative for fungal element and AFB, and cytology was normal. A fungal infection was suspected because of his immunocompromised state and not responding to treatment, thus he was started on oral voriconazole (400 mg BID for 1 day then 200 mg BID) and prophylactic valganciclovir. Tazocin was replaced by meropenem, as inflammatory markers continued to be high. On day 25 he was still febrile and was having occasional episodes of hemoptysis, so a repeat dose of methylprednisolone pulse was given. Creatinine was rising and a repeat renal ultrasound was suggestive of graft rejection and no perinephric collection. Cyclophosphamide 500 mg OD was started. On day 30, Blood CMV PCR was 2.609 DNA copies/ml and he was started on IV ganciclovir. Voriconazole was stopped but meropenem was continued. The patient's father declined renal biopsy at this time. On day 40 he developed flank pain and mild

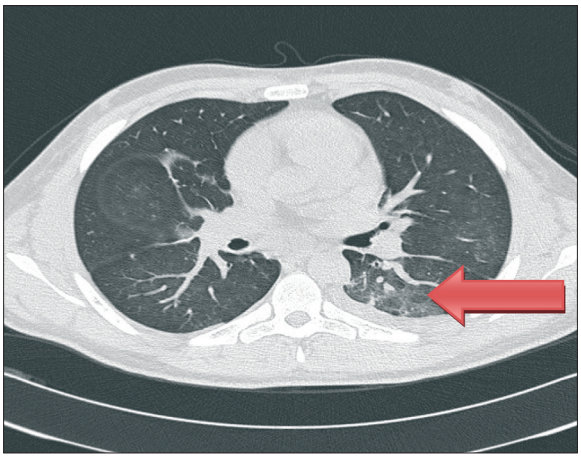

Figure 1. CT chest: patchy density of left lower lobe as indicated by arrow.

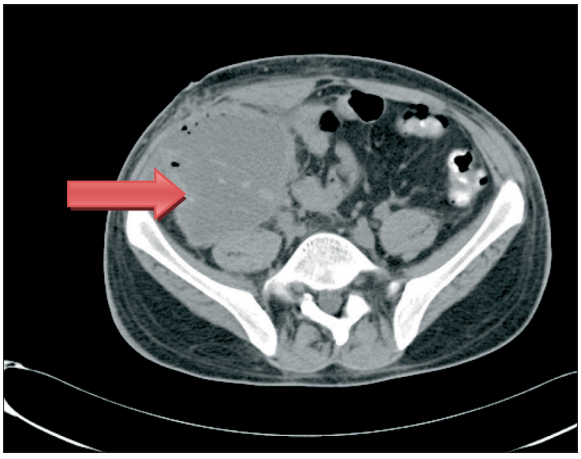

Figure 2. The CT abdomen showed big right iliac fossa abscess as indicated by the arrow.

hematuria along with fever. CT abdomen showed enlarged transplanted kidney with mixed density. Graft nephrectomy was done and intra-operative findings showed a swollen, necrotic, and friable graft with minimal pus. Five days post-procedure, however, fever reoccurred with abdominal pain and discharge at the surgical site. CT abdomen showed right iliac fossa abscess (Figure 2).

The patient underwent wound exploration. Fluid sent from the abdominal collection grew aseptate fungus later identified as Zygomycetes species (further speciation was not done). Histopathology of the excised kidney showed aseptate 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 pseudoaneurysm at the right pyriformis muscle region (Figure 3). Non-contrast MRI showed right-sided sacroiliitis with aneurysm, which was seen in one of the branches of the internal iliac artery. He underwent embolization, but post-procedure he had severe abdominal pain for which an urgent CT angiogram showed a large hematoma below the lower side of the anterior abdominal wall, with active bleeding in the previous collection. He underwent urgent exploration with finding of rupture of the right internal iliac artery

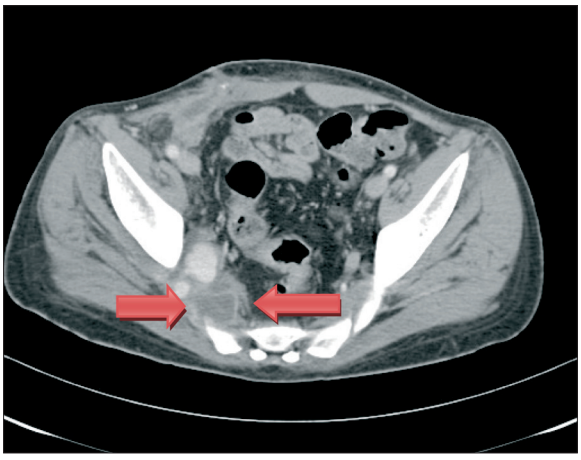

Figure 3. Abdominopelvic CT showed psueanerysm at right pyriformis muscle region as shown by the arrows.

aneurysm with necrotic tissues and pus. Posaconazole 400 mg BID was added to liposomal Amphotericin. His fever subsided 1 week later and he was discharged at day 90. On further follow-up in the outpatient department the patient improved clinically and radiologically. He received a total of 6 weeks of AmBisome and 12 weeks of oral Posaconazole with 2 weeks overlap between them.

Discussion

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 hematological malignancies [1,2]. Other underling diseases for this lethal infection are: diabetes mellitus, metabolic acidosis, treatment with glucocorticoids, solid organ transplant [2], treatment with Deferoxamine, iron overload, AIDS, injection drug use, trauma and malnutrition.

In a review of 116 solid organ transplant recipients with zygomycosis, most cases occurred in renal transplant recipients with similar clinical presentation among various types of organ transplantation, although patients with liver transplantation had a trend of higher incidence of dissemination (26.3%) (p=0.07) [3].

Marty et al. was first to describe an increased frequency of mucormycosis after voriconazole prophylaxis among recipients of allogenic HSCT. Subsequently, several retrospective series from geographically distinct transplant centers in the U.S. suggested an association between prior voriconazole exposure and subsequent development of mucormycosis [4]. In contrast, in a large prospective study comparing fluconazole and voriconazole for the prevention of invasive fungal infections, 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 infections 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 epidemiological link, or rather represents a marker of changing immunosuppression occurring in parallel with the evolution of transplant practices and immunosuppression strategies [4].

Zygomycetes are angioinvasive, causing infarction of infected tissues. Histologically, characteristic aseptate broad (5–50 µm) hyphae with propensity for invasion of blood vessels are seen. Our patient presented with cough and hemoptysis; it is likely that he had pulmonary zygomycosis that was not diagnosed, although his BAL was cultured for fungal infection as well as cytology, and all results were negative. Despite the ability of these organisms to invade tissues, they are rarely isolated from cultures of blood, urine, cerebrospinal fluid, feces, sputum, and paranasal sinuses secretions, bronchoalveolar lavage or swabs from infected areas. The recovery of zygomycetes from biopsy material may be compromised if the processing of the specimens involves tissue grinding, a procedure that kills the non-septate hyphae of these fungi. Combining microscopy and culture will increase the diagnostic yield by 15–20% [5]. Our patient received voriconazole for almost 3 weeks, which possibly contributed 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 intervention 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 doses, which can result in renal toxicity. Currently, liposomal Amphotericin B is frequently used for treatment of zygomycosis 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 patients with zygomycosis, highlighting posaconazole as promising treatment of these infections [6].

Our patient improved with surgical intervention and salvage treatment with posaconazole. The optimal duration of antifungal treatment for Zygomycosis remains an unresolved issue, hence treatment duration should be determined on an individual basis, but therapy usually continues for at least 6–8 weeks [7].

Conclusions

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

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