

Rhinomaxillary Mucormycosis in a Renal Transplant Recipient: Case Report

Negar Azarpira,¹ Mohamd Javad Ashraf,² Kouros Kazemi,³ Bighan Khademi⁴

Abstract

Objectives: Rhinomaxillary mucormycosis is a clinical manifestation of zygomycosis in solid-organ transplant recipients. Without proper diagnosis and treatment, rhino-orbital-cerebral zygomycosis, particularly a central nervous system disease, will develop with substantial complications.

Case report: A 42-year-old man who had undergone renal transplant was admitted to our otolaryngology department with unilateral bloody nasal discharge. Mucormycosis was detected in the necrotic tissue of the maxillary sinus. Surgical ablation of the infected parts, along with antifungal treatment, restricted extension of the infection.

Conclusions: Early detection of opportunistic infections in transplant recipients plays an important role in preventing dissemination. Fungal infections, including zygomycosis, should be considered in all solid-organ recipients, especially in persons with local unusual manifestations. Early diagnosis and successful treatment reduce mortality.

Key words: Kidney, Zygomycosis, Immunosuppression, Fungal, Infection

Introduction

Transplant recipients receive immunosuppression, have defects in cell-mediated immunity, and are

From the ¹Organ Transplant Research Center, ²Pathology Department, ³Transplant Center, and ⁴Otolaryngology Department, Shiraz University of Medical Sciences, Shiraz, Iran

Acknowledgements: N.A. and M.J.A. participated in the final pathologic diagnosis. K.K. participated in transplant surgery, and B.K.H. operated on the patient in the ENT department. All authors participated in the writing of the paper. We are also grateful to the Transplant Research Center, Shiraz University of Medical Sciences, for funding and support of this project. None of the authors have any conflicts of interest to declare.

Corresponding author: Negar Azarpira, MD, Organ Transplant Research Center Pathology Department, Nemazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran
Phone: +98 711 647 4331 Fax: +98 711 647 4331 E-mail: negarazarpira@yahoo.com

Experimental and Clinical Transplantation (2012) 6: 605-608

susceptible to infections with intracellular microorganisms such as toxoplasmosis, herpes virus, and fungal species.¹ An intact T lymphocyte-macrophage system is necessary to eradicate these infections. Induction therapy with antilymphocyte antibodies or high-dose corticosteroids for allograft rejection adds an additional defect to humoral immunity.^{1,2} Zygomycosis (mucormycosis) is an invasive opportunistic fungal infection. Diabetes mellitus, immunodeficiency, neutropenia, and malignancy are the main underlying conditions.

Mucormycosis may appear in different clinical forms, that is, rhino-cerebral, pulmonary, disseminated, gastrointestinal, and cutaneous.³ Use of immunosuppressive drugs obscure typical signs of infection. In transplant patients, diagnosis of this opportunistic infection is difficult.^{4,5}

Here, we present a histopathologically proven case of rhinomaxillary mucormycosis in a renal transplant recipient who presented with bloody nasal discharge. The patient was treated successfully.

Case Report

A 42-year-old man underwent a renal transplant from a brain-deceased donor in 2009. The postoperative course was uneventful. In June 2011, the patient was admitted to our center for headache and bloody nasal discharge. He did not have any risk factors such as diabetes mellitus, intravenous drug abuse, blood transfusion, neutropenia, or prior systemic/local infections.

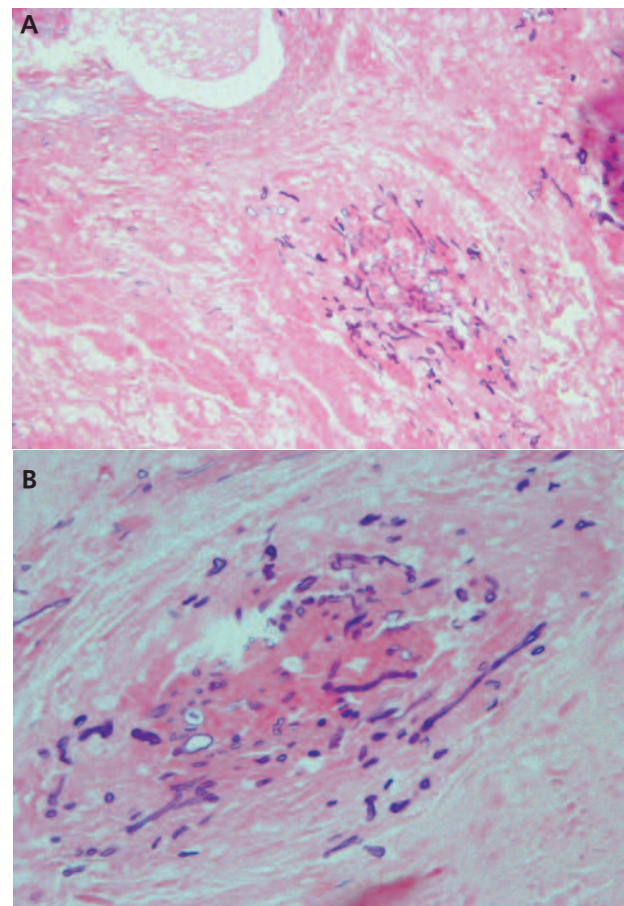
Immunosuppression protocol consisted of tacrolimus and mycophenolate mofetil. No abnormalities were found on an initial physical examination. Visual acuity, optic discs, and pupillary reaction were normal. Graft function was stable with a serum creatinine concentration of 159.12 $\mu\text{mol/L}$. The trough level of tacrolimus was 12.1 ng/L.

Water's view revealed diffuse radiopacity over the left maxillary antrum extending into the left nasal cavity. A computed tomography scan revealed left maxillary sinus opacification. A nasal endoscopy was performed, and an unusual mass under the middle concha with mucosal necrosis was revealed. Specimens of the paranasal sinus mucosa were sampled. Pathologic examination showed diffuse necrosis; thrombotic blood vessels with large, nonseptated fungal hyphae suggestive of mucormycosis (Figure 1A, 1B), as later confirmed by mycological culture. Medical treatment with intravenous conventional amphotericin B deoxycholate (1.5 mg/kg/d) was initiated. The patient underwent extensive endoscopic surgical debridement of the maxillary sinus. The immunosuppressive regimen was not reduced during hospitalization. A rise in serum creatinine level (176.80 $\mu\text{mol/L}$) after amphotericin B infusion developed. Liposomal amphotericin B with a lesser cytotoxic effect was the best choice for substitution, but unfortunately was not available. Therefore, the amphotericin B deoxycholate with a lower dosage was continued until complete resolution of infection. The fungal involvement was controlled and its extension fully stopped.

Discussion

Mucormycosis is a fungal infection owing to organisms in the order Mucorales and belonging to the general class of Zygomycetes. It is the third most-common invasive, fungal infection; after aspergillosis and candidiasis. It is usually found in soil, bread molds, decayed fruits, and vegetables, and also can be cultured from the nasal cavity, the throat, the oral cavity, and the stools of healthy patients. Everybody is exposed to this infection and inhales the spores; the nasal ciliary system transports these spores down in the pharynx where it is finally cleared in the gastrointestinal tract. The spores inhaled by the lungs are cleared by the phagocytes.⁶ In immunocompromised hosts, the infection begins in the middle and inferior nasal turbinates. From the nasal cavity, the infection spreads to the paranasal sinus and retro-orbital region via direct extension or local vasculature (rhinomaxillary mucormycosis). The fungus also spreads to the brain through the cribriform plate (rhinocerebral mucormycosis).^{7,8}

Figure 1. Aseptate Hyphae With Wide-Angle Branching in The Wall of Thrombosed Blood Vessel With Extensive Necrosis (H&E $\times 100$)



Rhinomaxillary is a localized form but without appropriate treatment, rhinocerebral mucormycosis may be developed.^{7,8} The major risk factors for mucormycosis are hematologic malignancy, neutropenia, pharmacologic immunosuppression, chemotherapy and corticosteroid therapy, diabetes mellitus (types 1 and 2), burns, penetrating trauma, and malnutrition.^{2,3,6} Because it is rare in transplant patients, a high index of suspicion is required. The diagnosis is based on history, clinical examination, radiologic findings, and tissue biopsy.²

Typical histologic hallmarks in hematoxylin-eosin staining are wide, ribbonlike aseptate hyphae, with wide-angle branching within necrotic material.² Invasion of the blood vessels, thrombosis with multiple infarctions, and hemorrhages are other important histologic findings of mucormycosis.^{2,3,7-10}

A fungal stain (eg, Gomori methenamine silver) also is helpful if the fungus is not easily found.^{1,9,11} In immunocompromised patients, these pathologic

changes are usually associated with minimal inflammatory response.^{9,11,12}

Patients are usually treated with amphotericin B deoxycholate. However, the major toxicities associated with amphotericin B are nephrotoxicity and infusion-related events (chills and fever).^{13,14} The liposomal amphotericin B is less nephrotoxic, with comparable effectiveness relative to amphotericin B deoxycholate. The lipid products might be advantageous, because higher doses per unit body weight can be used while preserving renal function. These products are usually recommended in patients who are refractory to, or intolerant of, commercial amphotericin B deoxycholate.^{14,15} Because amphotericin B cannot distribute itself through necrotic tissues, local debridement of infected structures is necessary.¹⁵

Our patient was a kidney allograft recipient with a predisposing factor of immunosuppression. He was treated with amphotericin B and aggressive surgical debridement. The outcome was excellent with survival of the patient and the graft.

The high index of suspicion and aggressive surgical treatment is crucial for early diagnosis with good outcomes. Suspicion index can be increased through recognition and understanding of the differential patterns of clinical presentation. Treating a patient's underlying medical condition, rapid correction of metabolic abnormalities and reducing immunosuppression, if feasible, are essential for successful treatment.¹⁶

There are few reports of survival in cases of mucormycosis affecting kidney transplant recipients.¹⁷⁻²¹ In a review of 106 cases, the overall mortality was 49%, and the rhino-sino-orbital disease had the best prognosis. In another study, the lowest mortality rate¹ was reported in cutaneous mucormycosis (16%), rhinocerebral (67%), pulmonary (83%), gastrointestinal, and the disseminated form was associated with 100% mortality rate.¹

Einollahi and associates reported that rhinocerebral type was the most-common form of disease, followed by pulmonary in kidney transplant recipients. The overall mortality rate was 52%. The mortality rate was 100% in recipients with pulmonary infection and low (30.8%) in the rhino-cerebral form of disease.²² Data from the Transplant Associated Infection Surveillance Network showed that among 1063 solid-organ

transplant recipients, mucormycosis represented 2% of invasive fungal infections.¹ In solid-organ transplant recipients, dissemination to distant organs seems occur more frequently after rejection and its treatment.^{1,16}

In conclusion, opportunistic fungal infections should be suspected in transplanted recipients. The short interval between demonstration of the primary limited clinical findings and the invasive surgical-medical treatment reduces the risk of mortality and morbidity.

References

1. Almyroudis NG, Sutton DA, Linden P, Rinaldi MG, Fung J, Kusne S. Zygomycosis in solid organ transplant recipients in a tertiary transplant center and review of the literature. *Am J Transplant.* 2006;6(10):2365-2374.
2. Singh N, Aguado JM, Bonatti H, et al. Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome. *J Infect Dis.* 2009;200(6):1002-1011.
3. Prabhu RM, Patel R. Mucormycosis and entomophthoromycosis: a review of the clinical manifestations, diagnosis and treatment. *Clin Microbiol Infect.* 2004;10(suppl 1):31-47.
4. Aslani J, Eizadi M, Kardavani B, et al. Mucormycosis after kidney transplantations: report of seven cases. *Scand J Infect Dis.* 2007;39(8):703-706.
5. Van der Westhuijzen AJ, Grotepass FW, Wyma G, Padayachee A. A rapidly fatal palatal ulcer: rhinocerebral mucormycosis. *Oral Surg Oral Med Oral Pathol.* 1989;68(1):32-36.
6. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis.* 2005;41(5):634-653.
7. Ashraf MJ, Azarpira N, Badiie P, Khademi B, Shishegar M. Fungal characterization using polymerase chain reaction in patients with fungal sinusitis. *Indian J Pathol Microbiol.* 2011;54(2):415-417.
8. Azarpira N, Esfandiari M, Bagheri MH, Rakei S, Salari S. Cerebral aspergillosis presenting as a mass lesion. *Braz J Infect Dis.* 2008;12(4):349-351.
9. Davari HR, Malekhossini SA, Salahi HA, et al. Outcome of mucormycosis in liver transplantation: four cases and a review of literature. *Exp Clin Transplant.* 2003;1(2):147-152.
10. Leitner C, Hoffmann J, Zerfowski M, Reinert S. Mucormycosis: necrotizing soft tissue lesion of the face. *J Oral Maxillofac Surg.* 2003;61(11):1354-1358.
11. Godara SM, Kute VB, Goplani KR, et al. Mucormycosis in renal transplant recipients: predictors and outcome. *Saudi J Kidney Dis Transpl.* 2011;22(4):751-756.
12. Neofytos D, Horn D, Anaissie E, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. *Clin Infect Dis.* 2009;48(3):265-273. Erratum in: *Clin Infect Dis.* 2009;48(5):690.
13. Sun HY, Forrest G, Gupta KL, et al. Rhino-orbital-cerebral zygomycosis in solid organ transplant recipients. *Transplantation.* 2010;90(1):85-92.
14. Allen U. Antifungal agents for the treatment of systemic fungal infections in children. *Can J Infect Dis Med Microbiol.* 2010;21(4):e116-e121.
15. Kontoyiannis DP, Lewis RE. How I treat mucormycosis. *Blood.* 2011;118(5):1216-1224.
16. Petrikos G, Drogari-Apiranthitou M. Zygomycosis in immunocompromised non-Haematological Patients. *Mediterr J Hematol Infect Dis.* 2011;3(1):e2011012.
17. Badiie P, Alborzi A. Invasive fungal infections in renal transplant recipients. *Exp Clin Transplant.* 2011;9(6):355-362.

18. Ladurner R, Brandacher G, Steurer W, et al. Lessons to be learned from a complicated case of rhino-cerebral mucormycosis in a renal allograft recipient. *Transpl Int.* 2003;16(12):885-889.
19. Chkhotua A, Yussim A, Tovar A, et al. Mucormycosis of the renal allograft: case report and review of the literature. *Transpl Int.* 2001;14(6):438-441.
20. Chacko B, David VG, Tamilarasi V, Deepti AN, John GT. Pulmonary mucormycosis in a nondiabetic renal allograft recipient successfully managed by medical therapy alone. *Transplantation.* 2007;83(12):1656-1657.
21. Tobón AM, Arango M, Fernández D, Restrepo A. Mucormycosis (zygomycosis) in a heart-kidney transplant recipient: recovery after posaconazole therapy. *Clin Infect Dis.* 2003;36(11):1488-1491.
22. Einollahi B, Lessan-Pezeshki M, Aslani J, et al. Two decades of experience in mucormycosis after kidney transplantation. *Ann Transplant.* 2011;16(3):44-48.