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Mucormycosis after Living Donor Kidney Transplantation: A Multicenter Retrospective Study

Pedram Ahmadpour[1], Mahboob Lessan-Pezeshki[2], Mohammad Hassan Ghadiani[3*], Fatemeh Pour-Reza-Gholi[1], Fariba Samadian[1], Jafar Aslani[4], Heshmatollah Shahbazian[5], Mohammad Reza Ghanji[2], Ammir Hossein Miladipour[1], Nader Nouri-Majalan[6]

[1]Department of Nephrology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Department of Nephrology, Tehran University of Medical Sciences, Tehran, Iran

[3]Legal Medicine Organization of I.R.I, Tehran, Iran

[4]Department of Pulmonary, Baqiyatallah University of Medical Sciences, Tehran, Iran

[5]Department of Nephrology, Ahwaz University of Medical Sciences, Ahwaz, Iran

[6]Department of Nephrology, Yazd University of Medical Sciences, Yazd, Iran

Abstract

Background and Aims: Mucormycosis is an extremely rare and potentially fatal complication after kidney transplantation. Limited data are available on mucormycosis following living donor kidney transplantation. The aim of this study was to determine the incidence of mucormycosis and to identify the clinical presentation and mortality rate in renal allograft recipients.

Methods: We conducted a retrospective survey of 7132 Iranian renal transplant recipients to find those with Mucormycosis in eight transplant centers from January 1990 to June 2008. A total of 22 patients had received kidneys from living donors were complicated with Mucormycosis. Mean follow up period after diagnosis was 9±13 (1-60) months.

Results: No significant differences were found between infection occurrence and gender (P=0.6). Patients with mucormycosis were older than those who had no infection (p=0.02) with the mean age at diagnosis 48 ± 13 years. The diagnosis time since transplantation ranged from 1-84 (Median: 12) months. Mucormycosis was most likely to occur within 1 year after renal transplantation (n=13). The major form of disease in population studied was rhino-cerebral (n =11), followed by pulmonary (n=8), cutaneous (n=2), and disseminated (n=1). In addition, 9 patients have had the history of steroid pulse therapy. Diabetes mellitus was seen in 6 recipients with mucormycosis.

Conclusions: To our knowledge, the current study is the largest sample of renal recipients with mucormycosis in living donor renal transplantation. Augmented immunosuppression, especially with corticosteroids, older age and PTDM were the predisposing factors for the infection.

Keywords: Renal Transplantation, Mucormycosis, Living Donor, Multicenter Study

Introduction

Mucormycosis represents a small amount of invasive fungal infections (IFIs) in solid organ transplants. In renal allograft recipients it is an extremely rare condition with incidence of 0.2 -1.2 % (1, 2). It is

*Correspondence:
Hassan Ghadiani, MD
Legal Medicine Organization of I.R. Iran Behesht St. Tehran -Iran
Email: mhghadiani@yahoo.com
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a rapidly fatal complication, particularly if the patients had earlier received aggressive anti-rejection therapy (2-6). Renal transplant recipients are at high risk for mucormycosis because of chronic immunosuppression, frequent use of broad-spectrum antibiotics, and underlying metabolic disorders such as uremia and post-transplant diabetes mellitus (PTDM) (1). In a recent study involving a series of 2878 solid organ transplants, performed between January 1995 and December 2006, a shift towards non-aspergillus filamentous fungal infections (nAFFI) was observed with eight out of eleven cases having nAFFI mucormycosis (7). In addition, in a series of 21 renal recipients with IFIs in our centers, Mucormycosis accounted for 52% of all invasive mycoses and was associated with mortality rate as high as 72.7% (8).

These fungi can cause a variety of infections in humans, including rhinocerebral (6), pulmonary (9), gastrointestinal (10), cutaneous (11) and allograft (12). Almost all patients with invasive zygomycosis or mucormycosis have some underlying disease that predisposes the patient to infection and also influences the clinical presentation. The most common underlying conditions are: Diabetes mellitus, metabolic acidosis, treatment with glucocorticoids, hematologic malignancies, and solid organ transplantation (4, 5, 13).

Although, Iran has the largest reported experience of living unrelated donor transplants (14), there are limited data available on mucormycosis following transplantation in Iran (5, 11, 15). Therefore, a large retrospective study was conducted on 7132 Iranian renal transplant recipients to determine the incidence of mucormycosis and to identify the clinical presentation and mortality rate following kidney transplantation.

Materials and Methods

The current study is a retrospective survey of 7132 Iranian renal transplant recipients to find those with mucormycosis from eight transplant centers between Jan 1990 and Jun 2008. A total of 22 patients who received kidneys from living donors were complicated with mucormycosis. Data gathered included age, sex, date of transplantation, total number of operations, immunosuppressive regimen, graft rejection episodes, date of diagnosis, organs affected by infection, treatment and patient's outcome.

Their maintenance immunosuppression regimen was cyclosporine in all recipients; 8 patients received cyclosporine, azathioprine, and prednisone; while 13 recipients were on cyclosporine, mycophenolate mofetil, and prednisone; and one received cyclosporine and prednisone.

Suspicion of diagnosis was based on clinical presentation, radiological findings and unresponsiveness of infections to conventional antibiotic therapy. For suspected cases of pulmonary involvement, fibreoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB) were performed.

Materials from TBB were embedded in paraffin blocks, and sections of 5 mm stained with haematoxylin and eosin. BAL fluids were cytocentrifuged and stained with Papanicolaou and Gomori methenamine silver stains. BAL fluids were also sent for bacterial, fungal, viral, and mycobacterial cultures. Fungal cultures were incubated at 30^{o}C for at least 4 weeks. Plates were evaluated daily for the first 7 d and at least twice per week thereafter. Diagnosis of mucormycosis was made in the presence of at least 1 of the following criteria (5): 1) histopathological evidence of tissue invasion on tissue biopsy; 2) positive culture from a deep tissue specimen such as blood, CSF, or biopsy specimen; 3) At least 3 positive sputum smears for pseudohyphae and budding yeast and/or positive sputum culture with clinical findings consistent with pneumonitis resistant to broad-spectrum antibiotics. Treatment of mucormycosis consisted of antifungal therapy in combination with surgical debridement of affected tissues. All patients with mucormycosis were treated with intravenous amphotericin B.

The initial dose was 0.5 mg/kg that was gradually

increased to 1-1.5 mg/kg with total doses of 2-3 g. Seventeen patients with mucormycosis underwent surgery for debridement or pulmonary resection, the rest died before surgical procedure. Mean follow up period after diagnosis was 9±13 (1-60) months.

Statistics:

SPSS version 15.0 was used for data analyses. Qualitative variables were expressed as number and percentage, while quantitative variables were expressed as mean ± standard deviation (SD). Proportions were compared by Chi-square and Fishers' exact tests. Continuous variables were compared using the Student's *t*-test. All statistical tests were performed at the 0.05 significance level.

Results

Mucormycosis infection developed in 22 recipients (0.3%), 13 male and 9 female. There was no significant difference between infection occurrence and gender (P=0.6). Patients with mucormycosis were older than those had no infection (Table 1).

The mean age of patients at diagnosis was 48 ± 13 (ranged from 19 to 71) years, only 5 cases were under 40 years old. The time to diagnosis since transplantation ranged from 1 to 84 (Median: 12) months. Mucormycosis was most likely to occur within 1 year after renal transplantation (n=13). The major form of disease in population studied was rhino-cerebral (n =11), followed by pulmonary (n=8), cutaneous (n=2), and disseminated (n=1). There was no significant difference between recipients received mycophenolate mofetil or azathioprine (P = 0.9). In addition, 9 patients have had the history of steroid pulse therapy. Diabetes mellitus was seen in 6 recipients with mucormycosis.

Overall mortality rate in this series was 59%, particularly in recipients with pulmonary infection (100%). There was no statistically significant difference in mortality rate between male and female (P=0.6). The overall mortality rate did not change significantly over the time course of the study (P = 0.6). Acute rejection was only seen in one patient who survived despite withdrawal immunosuppression.

Although, lung involvement was seen in older recipients when compared to patients with rhino-cerebral involvement, however, there were no statistically significant differences between the age and the form of presentation (mean age were 50±10 and 44±17 year, respectively; P=0.3). Five cases with pulmonary infection and 3 patients with rhino-cerebral involvement occurred within 6 months after transplantation but no statistically significant differences was observed between time of presentation of infection after operation and sites of involvement (mean time were 17±28 and 36±27 months, respectively; P=0.19). On the other hand,

Table 1: Age, gender and immunosuppressive regimen data of the kidney recipients with and without Mucormycosis

	Mucor Group (n=22)	**Mon- Mucor Group** (n=7110)	P Value
Age in years at transplantation, yr mean (±SD)	46 ± 13	38 ± 16	0.02
Gender (Male/Female), n	13/9	4538/2572	0.6
MMF / AZA based immunosuppressive regimen, n	13/8	4462/2648	0.9

Mucor, Mucormycosis; **n**, number; **SD**, Standard Deviation; **yr**, years; **MMF**, Mycophenolate Mofetil; **AZA**, Azathioprine .

when the data of a female patient with pulmonary involvement after 84 months was omitted from this analysis, the differences between the two groups became significant (mean time were 8±9 vs 36±27 months; P=0.02).

Discussion

Mucormycosis refers to a spectrum of disease presentations caused by fungi of the class Zygornycetes, order Mucorales. These ubiquitous saprophytes are commonly found on decaying vegetation and in the soil (1). These fungi grow rapidly and release large numbers of spores that can become airborne. Although zygomycetes are common in the environment, but this fungal infection is a rare human infection due to the effectiveness of the intact human immune system (3). Augmented immunosuppression to treat rejection, mainly in the form of steroids, as was given to our patients may accelerate the course of mucormycosis infection. Furthermore, mucormycosis frequently occurred in older recipients compared to younger patients who previously did not have this fungal infection. In our review, most of the patients were in their 40s and only 5 cases were under 40 years of age. In a retrospective study of fungal infection in hematopoietic stem cell transplant recipients, it was found that age > 40 was a risk factor for invasive fungal infection with mucormycosis (16). PTDM was also another predisposing factor in some of our cases.

The predominant forms of presentation are rhino-cerebral, pulmonary, gastrointestinal, cutaneous and disseminated (17). The underlying medical condition and associated risk factors determine the type of mucormycosis that develops in a patient. In patients with haematological malignancy, pulmonary form, followed by disseminated and rhino-cerebral presentations, are the most common (18). In the current study, pulmonary mucormycosis in contrast with previous report (5) was the second most common form, accounting for more than 36% of all the infections.

Pulmonary mucormycosis is a rapidly progressive infection that occurs after inhalation of spores into the bronchioles and alveoli (19). Males appear to be over-represented in the medical literature, with a male to female ratio of 2.4-3: 1 (20); while in the present study this ratio for patients with pulmonary mucormycosis was 1.6:1. This predominance of male recipients is difficult to explain, and none of the risk factors explain it. The outcome in patients with pulmonary mucormycosis is worse than for patients with rhino-cerebral involvement, with mortality rates as high as 60–100 percent (4, 13, 20, 21). This may be in part due to the underlying conditions and to the inability to widely excise the involved tissues. In the present study, all patients with pulmonary infection died.

Disseminated mucormycosis involves two or more noncontiguous organs. The mortality rate for disseminated disease approaches 90 to 100 percent (13) and our patient with disseminated mucormycosis died as well.

Mucormycosis frequently occurred in the first year after renal transplantation, as in 59% of all of our patients. It is reported that 80% of cases in solid organ transplant recipients occurred within first 6 months of transplantation (22), and 36% in our involved recipients.

The prognosis of the rhino-cerebral form is relatively poor (4) and it must be suspected in a transplant recipient showing fever, maxillary swelling, and edema. Early diagnosis, aggressive surgical debridement, in conjunction with an intravenous amphotericin B and careful monitoring can be helpful in treating these patients and achieve favorable prognosis. Fortunately, mortality rate from rhino-cerebral involvement was reduced to as low as 36% in the current study.

Interestingly, the rate of acute rejection was not increased in surviving patients despite withdrawal or reduction of immunosuppression. We are of view that mucormycosis infection may also enhance immunosuppression after kidney transplantation

and, hence, can lead to decrease in susceptibility to allograft rejection.

Finally, primary cutaneous mucormycosis is a relatively rare entity with better prognosis in renal transplant patients. Our recipients with cutaneous form were completely cured (11).

Conclusions

To our knowledge, the current study is the largest sample of renal recipients with mucormycosis in living donor renal transplantation. Mucormycosis is an extremely rare complication of kidney transplantation. Augmented immunosuppression, especially with corticosteroids, older age and PTDM were the main predisposing factors for the infection. A high index of suspicion, leading to an early diagnosis, may be the key to an early initiation of therapy. Followed by prompt surgical debridement and antifungal therapy, it may result in a more favorable outcome.

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