Original Research Article

Study of systemic fungal infections in renal transplant recipients

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Abstract

Background: Despite technical, immunological, and therapeutic advances in the field of renal transplantation, infections remain a major barrier to successful outcome. Fungal infections (14%) after renal transplantation, despite a lower incidence than bacterial and viral infections, remain a major cause of morbidity and mortality. This study was conducted to assess the impact of invasive fungal infections in our renal transplant recipients.
Aim: To study the clinical profile, risk factors for acquiring fungal infections, its outcome and the factors influencing outcome in living and deceased donor renal transplant recipients.
Materials and methods: Renal transplant recipients both cadaveric and living-related during the time period between August 2008 and May 2011 admitted with systemic fungal infections in nephrology ward were included in the study. Data gathered included age, sex, date of transplantation, date of diagnosis, fungal pathogen, organs affected by infection, treatment and patient outcome. Microsoft excel 2007, Binomial and Student t tests were used for statistical analysis.
Observation: Twenty two patients were diagnosed with systemic fungal infections during this period. The mean age of the study patients was 35.55 years. The male to female ratio was 1.75:1.Candida species (62%) are the commonest organisms causing fungal infection. Fungal infections commonly occurred in gastrointestinal tract (GIT), lung and urinary tract, each 22%. Fifty percent of patients with fungal infections expired. Graft loss occurred in 41% of patients.
Conclusion: The mortality rate was 50%. Bone marrow suppression {Leukopenia (50%)} and hypoalbuminemia (59%) contributed to high mortality. Overall immunosuppression should be monitored periodically and kept at optimal level just enough to avoid rejection, thereby avoiding opportunistic infections.

Key words

Fungal Infection, Renal transplant recipients, Mortality, Candida species, graft loss.

Introduction

Two major factors for successful organ transplantation are better control of rejection and better prevention and treatment of infections [1]. Despite technical, immunological, and therapeutic advances in the field of renal transplantation, infections remain a major barrier to successful outcome. More than 80% of renal transplant recipients suffer at least one episode of infection within 1 year of transplantation [2]. Fungal infections after solid organ transplantation, despite a lower incidence than bacterial and viral infections, remain a major cause of morbidity and mortality [3]. As many as 14% of renal allograft recipients, 32% of heart recipients, 35% of heart lung, 38% of pancreas recipients and 42% of liver recipients have been reported to develop clinically significant fungal infections [4]. Among fungi, the responsible pathogens include Cryptococcus neoformans, aspergillus species, Candida species, Coccidioidomyces immitis, Histoplasma capsulatum and Mucormycosis. The occurrence of invasive fungal infections is highest in the early post transplant period, when immunosuppression is greatest. Prolonged antifungal therapy and surgical intervention are needed for control of fungal infections. This study was conducted to assess the impact of invasive fungal infections in our renal transplant recipients.

Aim

To study the clinical profile, risk factors for acquiring fungal infections, its outcome and the factors influencing outcome in living and deceased donor renal transplant recipients.

Materials and methods

Renal transplant recipients both cadaveric and living-related during the time period between August 2008 and May 2011 admitted with systemic fungal infections in nephrology ward were included in the study.

Detailed history, duration of post transplant status, nature of immunosuppression, duration and type of symptoms, and history of other co morbid illnesses predisposing to fungal infections like Diabetes Mellitus and viral infections like HIV, HCV and CMV were taken. Data gathered included age, sex, date of transplantation, date of diagnosis, fungal pathogen, organs affected by infection, treatment and patient outcome.

General examination and systemic examination followed by detailed examination of systems involved like eye, ENT, respiratory tract, GI tract etc, Were done.

Routine investigations like urinalysis & culture, complete hemogram, blood sugar, renal function tests, liver function tests, blood culture (bacterial and fungal), imaging of brain, Para nasal sinuses, thorax and abdomen (like X-ray, USG, CT scan) were done.

Invasive investigations for tissue diagnosis and cultures like UGI scopy, bronchoscopy, nasal endoscopy and cystoscopy and tissue biopsy were done after obtaining written informed consent from the patient.

Diagnosis was made by radiological findings, positive blood or bronchoalveolar lavage (BAL) cultures and tissue biopsies. For suspected cases of pulmonary involvement, fibreoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was performed. Materials from transbronchial biopsy were embedded in paraffin blocks, and sections of 5mm stained with hematoxylin-eosin. BAL fluids were cytocentrifuged and stained with Papanicolaou stain and Gomori methenamine silver stain. BAL

fluids were also sent for bacterial, fungal, viral and mycobacterial culture.

Speciments for fungal isolation are plated on inhibitory mold media, brain-heart infusion agar, and mycobiotic agar (Gibco Diagnostics, Madison, Wisc.) some fungi (Histoplasma capsulatum) can take up to 25 days to grow. Fungal cultures were incubated at 30˚C for at least 4 weeks. Plates were evaluated daily for the first 7 days and at least twice per week thereafter.

Diagnosis of invasive fungal infection was made in the presence of at least one of the following criteria: 1) histopathological evidence of tissue invasion on biopsy specimen; 2) positive culture from deep tissue specimen such as blood, cerebrospinal fluid (CSF), peritoneal fluid; 3) KOH mount of specimen showing pseudohyphae and/or budding yeast. For diagnosis of Cryptococcus, India ink preparation of the sample (CSF) was done.

In this study esophageal candidiasis was included as systemic fungal infection. It was diagnosed by upper GI endoscopy and histopathological examination of mucosal biopsy.

All the patients were treated with intravenous Amphotericin B deoxycholate with a maximum cumulative dose of 1.5 to 2 gms. Those who had sinusitis due to mucormycosis underwent sinus surgery. Esophageal candidiasis was also treated with intravenous Amphotericin B till a cumulative dose of 500 mg followed by repeat upper GI scopy. If esophageal candidiasis was persistent, another 500 mg of intravenous Amphotericin B was given.

In the above patients, etiology, clinical profile, risk factors, prognostic indicators and outcome were analyzed with appropriate statistical analysis.

Statistical methods

Microsoft excel 2007 was used to calculate mean. Binomial test was used to analyze factors predisposing the occurrence of fungal infections. Student t test was used for analyzing the factors influencing patient outcome. Differences were considered to be significant if the p-value was less than 0.05.

Results

This study was conducted between August 2008 and April 2011, in the Department of Nephrology, Government General Hospital, Chennai. Twenty two patients were diagnosed with systemic fungal infections during this period. The mean age of the study patients was 35.55 years. The male to female ratio was 1.75:1.The mean duration of disease before renal transplant for these patients was 16.5 years. And the mean dialysis duration was 7.8 years.

No significant co-morbidity was observed in 64% of the study population (**Tale – 1**).

Table - 1: Pretransplant co-morbidities in patients with fungal infections.

Co-morbidity	Number	Percentage
Diabetes mellitus	1	4.5
Systemic Lupus Erythematosus (SLE)	1	4.5
Liver disease	0	0
Human Immunodeficiency Virus (HIV)	0	0
Hepatitis B Virus (HBV)	1	4.5
Hepatitis C Virus (HCV)	1	4.5
Cytomegalo Virus (CMV)	0	0
Pulmonary Tuberculosis (TB)	2	9
Fungal infection	2	9
No co-morbidities	14	64
Total	22	100

77.5% of infections were noticed in living donor renal transplant recipients compared to deceased donor renal transplant recipients (22.5%). Among the twenty two patients with fungal

infections, 41% received Tacrolimus, Mycophenolate and Prednisolone. Thirty six percent received Cyclosporine, Azathioprine and Prednisolone. The rest received Cyclosporine, Mycophenolate and Prednisolone. Fifty five percent of fungal infections developed in patients with early graft dysfunction (within 3 months). Fifty five percent of patients developed fungal infections within 6 months. The mean time of presentation is 12 months (range 0.5-83 months).

Binomial test has been used for analyzing the **Table - 2** (p-value<0.05 is significant).

Table - 2: Factors predisposing the occurrence of fungal infections.

Factors	Present	Absent	Percentage	P-value
Graft Dysfunction (GDF)	20	2	91	0.001
Surgical problems	3	19	14	0.001
New onset diabetes after transplant (NODAT)	6	16	27	0.052
HBV	2	20	9	0.000
HCV	3	19	14	0.001
CMV	11	11	50	1.000
Bacterial infections	12	10	55	0.832
Anti Rejection Therapy	8	14	36	0.286
Leukopenia	11	11	50	1.000
Anemia (<11g/dl)	9	13	41	0.523
Thrombocytopenia	9	13	41	0.523

Graft dysfunction alone seemed to be the risk factor for the occurrence of fungal infection. Though many patients received anti rejection therapy (ART, 36%) and cytomegalovirus (CMV, 50%) and bacterial infections (55%), leukopenia (55%), anemia (41%) and thrombocytopenia (41%) were present in many patients, they did not seem to predispose to the occurrence of fungal infections. (No statistical significance).

Fungal infections commonly occurred in gastrointestinal tract (GIT), lung and urinary tract, each 22%. Other sites were upper respiratory tract (15%), blood stream (11%) and central nervous system (CNS, 8%).Fifteen of the twenty two patients underwent renal biopsy. Acute cellular rejection (29%) was the commonest histopathology followed by acute tubular necrosis. Candida species (62%) is the commonest organism causing fungal infection. The other organisms are Mucor (17%), Aspergillus (13%), Cryptococcus (4%) and Pneumocystis (4%).

Student t test was used for analyzing the **Table - 3**. P-value <0.05 was considered as significant.

Fifty percent of patients with fungal infections expired. Graft loss occurred in 41% of patients. Thirty two percent of patients continued to have stable graft dysfunction.

Leukopenia and Hypoalbuminemia influenced patient outcome by contributing to mortality (p value – 0.001). And also more significant number of deaths occurred in patients who received renal allograft from living donor (p value – 0.001).

Discussion

This study was conducted in the Department of Nephrology, Government General Hospital, Chennai during the period between August 2008 and April 2011. Twenty two patients were diagnosed with systemic fungal infections during this period.

Table - 3: Factors influencing patient outcome.

Parameter	Survived	Expired	P-value
Deceased donor	4	1	
Living donor	7	10	0.001*
DGF	4	3	0.666
ART	4	2	0.362
NODAT	4	2	0.362
CMV	5	6	0.687
Bacterial infection	7	5	0.416
Thrombocytopenia	3	6	0.211
Leukopenia	2	9	0.001*
Anemia	6	6	1
Serum Albumin <3.5gm/dI	3	10	0.001*
Graft dysfunction	9	11	0.152
Candida	7	7	1
Pneumocystis	1	0	-
Mucor	1	3	0.291
Aspergillus	2	1	0.557
Cryptococcus	0	1	-
Graft loss	3	6	0.211
Normal graft function	4	2	0.362
Stable graft dysfunction	4	3	0.666

The mean age of the study patients was 35.55 years. The male to female ratio was 1.75:1. In a 10 year study done in Iran (from 1998 to 2008), the mean age of patients was 49 yrs and the male to female ratio was 4.2:1 [5]. In a study by Chugh, et al., all patients were males with a mean age of 31.05±7.73 years (range 21-42 years) [6].

In our study, living donor renal transplant recipients acquired 77.5% of infections compared to deceased donor recipients (22.5%).

In our study, fifty five percent of fungal infections occurred within 6 months of renal transplantation. Sixty four percent of infections occurred within a year. According to Abbott et al, majority of the fungal infections occurred within 6 months [7]. In a study by Chugh, et al., infection occurred within the first year following transplantation in seven patients and after the first year in the others [6]. In a 10 year study done in Iran (from 1998 to 2008), 74% of invasive fungal infections occurred within 1 year. In another retrospective study (from 1987 to 1997) done in our department, out of 66 episodes of fungal infection 4 episodes occurred within 1 month; 28 between 1 and 6 months; and 37 after 6 months i.e., nearly 50% of the infections occurred within 6 months [8]. This phenomenon may be because of the use of numerous and higher doses of immunosuppressive agents.

In our study, Candida species (62%) are the commonest organisms causing fungal infection. The other common organisms are Mucor (17%) and aspergillus (13%). Cryptococcus and pneumocystis constituted 4% each. In a retrospective study done in our department, Candida was the commonest pathogen, causing 50 of the fungal infection episodes (72.5%). Aspergillus (11 episodes, 4.3%), and Mucormycosis (2 episodes, 2.8%) constituted the rest [8]. In the Iranian study, Mucormycosis (11/21) was the commonest infection followed by Candidiasis (4/21) and aspergillus (3/21) [5].

In a study by Fishman, et al., Candida and Aspergillus were the common organisms [9]. Infection with Cryptococcus neoformans was observed in eight patients (42%), Candida albicans in seven (37%), Mucor species in two (11%), aspergillus flavus in one (5.5%), and a mixed infection with Aspergillus and Cryptococcus in one patient (5.5%).

In our study, fungal infections commonly occurred in gastrointestinal tract (GIT), lung and urinary tract, each 22%. Other sites were upper respiratory tract (15%), blood stream (11%) and central nervous system (CNS, 8%). In a retrospective study done in our department, sites of infections were GI tract (35, 50.7%), respiratory tract (18, 26%), urinary tract (8, 11.5%), CNS (3, 4.3%), and graft (2, 2.8%) [8]. The sites of infection were almost similar to the in the present study.

In the literature, the risk factors for developing fungal infection in the post renal transplant setting were the following like deceased donor and retransplantation, older age, high doses of immunosuppression for anti rejection treatment, diabetes mellitus, CMV infection, bacterial infection with prolonged antimicrobial therapy, surgical interventions, indwelling catheters and anatomical abnormalities of the urinary tract [10]. In our study, graft dysfunction alone seemed to be a risk factor for the occurrence of fungal infection. Though many patients received anti rejection therapy (ART, 36%) and cytomegalovirus (CMV, 50%) and bacterial infections (55%), leukopenia (55%), anemia (41%) and thrombocytopenia (41%) were present in many patients, they did not predispose to the occurrence of fungal infections. (No statistical significance).

In a retrospective study done in our department, predisposing factors were anti-rejection therapy in 24 cases, bacterial infections in 19, leukopenia in 12, tuberculosis in 7, and CMV infection in 5 [8]. This difference may be due to the small number of patients in the present study. In a study by Chugh, et al., graft function was normal at the time of diagnosis in 13 patients (68%) while it was impaired (serum creatinine 160umol/l) in six patients (32%) [6].

In the retrospective study done in our department, Six out of 10 diabetic recipients developed fungal infections [8]. But in our study, only one patient had pre transplant diabetes mellitus. He developed fungal infection in the post transplant period. In a study by Chugh, et al., apart from immunosuppressive drugs, predisposing factors included post-transplant diabetes mellitus in two and leukopenia in two patients. Concomitant bacterial infections were present in seven patients [6].

In our study 50% (11/22) of patients with fungal infection died. In the retrospective study done in our department, a total of 36 out of 60 patients with fungal infection died (mortality 60%) [8].

In our study, high percentage of deaths occurred in patients with mucormycosis (75%, 3 of 4); all of them had rhino cerebral Mucor with GDF, post transplant diabetes mellitus and leukopenia. 50% of patients with Candida infections died. Three had blood stream and urinary tract infections, the remaining 4 deaths were due to Candida UTI and bacterial sepsis. All those patients who had Candida esophagitis survived. Thirty three percent of patients with Aspergillus (1 out of 3) and 100% of cryptococcal meningitis patients died (one patient). In the Iranian study, 52.4% (11/21) of patients died due to fungal infection, mostly due to Mucormycosis (74%) [5]. Leukopenia (11/22, 50%) and hypoalbuminemia (13/22, 59%) influenced patient outcome by contributing to mortality. And also more significant number of deaths occurred in patients who received renal allografts from living donor (10 out of 17, 59%). Their association was statistically significant.

Conclusion

In our study majority (64%) of fungal infections occurred in the first year, with Candida as the commonest fungal pathogen. Those who had

prior graft dysfunction developed fungal infections. The mortality rate was 50%. Bone marrow suppression {Leukopenia (50%)} and Hypoalbuminemia (59%) contributed to high mortality. Overall immunosuppression should be monitored periodically and kept at optimal level just enough to avoid rejection, thereby avoiding opportunistic infections.

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