Invasive Fungal Infections in Renal Transplant Recipients

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In a retrospective analysis, 18 instances of invasive fungal infections were observed in 512 (3.5%) renal transplant recipients. These included candidiasis (8), aspergillosis (5), cryptococcosis (3) and zygomycosis (2). All patients with candidiasis had Candida isolated from blood and one or more additional sites. One of them had superadded fungaemia with Torulopsis glabrata. Pulmonary disease in four and subcutaneous infection in one were encountered in the five patients with aspergillosis. Central nervous system involvement in two and cutaneous lesion in one were the findings in patients with cryptococcosis. Zygomycosis involved the lung in one and the allograft itself in the other. Prolonged fever not responding to antibacterial drugs was the most common clinical presentation. Fungal infections occurred during the first 4 months in 10 (55.5%) and 12 to 108 months in eight (44.5%) patients. Infections with cytomegalovirus and hepatitis viruses were concommitantly present in 12 (66.7%) and eight (44.5%) patients respectively. Fourteen episodes of fungal infections (77.8%) occurred in live unrelated kidney recipients who formed only 48% of our total transplant population. Nine patients were treated with systemic and/or local amphotericin B and six with amBisome. Fluconazole was administered alone in three and in combination with amphotericin B in two. Fourteen patients died but mortality was only directly attributable to fungal infection in 11. We conclude that invasive fungal infections continue to be an important cause of morbidity and mortality in renal transplant recipients. A high index of suspicion, prompt diagnosis and early institution of specific antifungal therapy are needed.

Introduction

The quality of life and graft survival after kidney transplantation have greatly improved since the introduction of cyclosporin. However, infection still remains a major cause of morbidity and death. Amongst the different types of severe infections following kidney transplantation, those caused by fungi carry the highest mortality despite having a lower incidence than bacterial or viral infections.[1] Difficulty in early diagnosis, low index of suspicion, lack of effective therapy in certain fungal infections, limited information on effective antifungal prophylaxis and severe toxicity associated with antimycotic therapy may contribute to the high mortality associated with these opportunistic infections. Although, several studies have reported on fungal infections following renal transplantation,[2–7] such information is lacking from this part of the world. This prompted us to review our renal transplant recipient population for invasive fungal infections and report their occurrence, spectrum and salient clinical features.

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Materials and Methods

Study population and diagnostic criteria

We retrospectively reviewed case charts of 512 renal transplant recipients on follow up from January 1989 to January 1995 in Mubarak Al-Kabeer Teaching Hospital, Kuwait. Two hundred and fifty (48.8%) patients had received live related kidneys, 248 (48.4%) live unrelated and 14 (2.8%) cadaver. The diagnosis of invasive fungal infection was based on the isolation of the aetiologic agent from appropriate clinical specimen(s) and/or its demonstration on direct microscopy/histopathology. Detection of the antigen in serum/CSF provided additional diagnostic evidence in patients with cryptococcosis. Patients with only superficial fungal infections were excluded. Bacteriological, virological and serological tests were reviewed in search for other concomitant infections. All cases had chest X-rays while CT-scan of brain was performed only when there was headache or any other central nervous system symptom or finding. In addition, information on age, sex, immunosuppressive therapy, preinfection rejection episodes, type of donor, clinical presentation, site of disease, source of the diagnostic material, concurrent illnesses/infections, antimicrobial

therapy, outcome, duration of follow-up and recurrence were also recorded.

Immunosuppressive therapy and prophylaxis

Most renal transplant recipients were on triple drug immunosuppression with prednisolone (1 mg/kg tapered to 10 mg/day in 6 months), cyclosporine A (7 mg/kg/day tapered to 1–2 mg/kg/day in 6 months) and azathioprine (1–1.5 mg/kg tapered to 1 mg/kg/day in 6 months). Monoclonal anti-T-cell antibody (OKT3) and anti-lymphocyte globulin (ALG) were not used in the induction protocol. Intravenous methyl prednisolone pulses and/or OKT3 were used in the treatment of rejection episodes. All patients had prophylactic oral nystatin, trimethoprim-sulphamethoxazole and acyclovir regularly for the first 6 months after transplantation.

Antifungal therapy

The antifungal treatment mainly consisted of intravenous amphoterecin B, amBisome, and oral/intravenous fluconazole. Rifampicin was used in combination with amphoterecin B in two instances. 5-Fluorocytosine was not used as it was not locally available. Amphotericin B was given in a dose of 0.5–1.5 mg/kg/day and amBisome 1–3 mg/kg/day. The dose of fluconazole was 200 mg intravenously daily or 200–400 mg/day orally. The duration of therapy varied from 2 weeks to 6 months depending on the clinical status and therapeutic response.

Laboratory evaluation

Histopathological and microbiological evaluation was undertaken on all clinical specimens. microscopic examination of specimens included wet mount, KOH preparation, Gram's stain, Ziehl-Neelsen stain and modified Kinyoun stain. Histopathologic sections were stained with haematoxylin-eosin, periodic acid Schiff, methenamine silver and Gram-stains. The specimens were routinely cultured onto blood, chocolate, MacConkey, Columbia nalidixic acid and charcoal-yeast extract agar and all cultures were incubated in 5% CO_2 (except those on MacConkey agar which were incubated in ambient air) at 35°C for 48 h. Clinical specimens processed by the mycology laboratory were routinely cultured on Sabouraud agar with and without chloramphenicol (50 mg/l) and incubated up to 6 weeks.
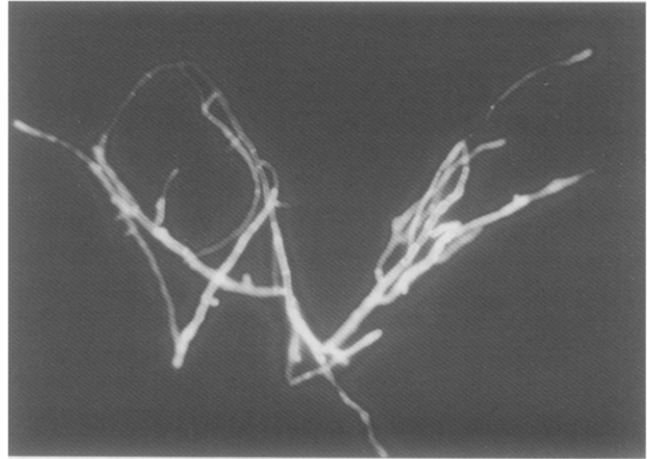

Figure 1. Dichotomously branched, septate hyphae of *Aspergillus favus* from bronchoalveolar lavage of Case 17. KOH-Calcofluor white preparation × 570.

Results

Systemic fungal infections were diagnosed in 18 out of 512 (3.5%) renal transplant recipients. These included candidiasis in eight (44.4%), aspergillosis in five (27.8%), cryptococcosis in three (16.6%) and zygomycosis in two (11.2%). None had mixed fungal infections except one who had both *C. albicans and T. glabrata*. There were 12 males and six females. The salient clinical and laboratory details of these cases are shown in Tables I and II. The time of onset of fungal infection varied from 2 weeks to 108 months (25.3 ± 33 months) after transplantation. The graft function was normal in six (33.3%) and mildly impaired in eight (44.4%, Serum creatinine 121–300 umol/l) and moderate to severe often requiring dialysis in four (22.2%). Fourteen patients were on triple immunosuppression with prednisolone, cyclosporin and azathioprine, two on cyclosporin and prednisolone and one on azathioprine and prednisolone combination. Eight patients had acute rejection episodes requiring anti-rejection treatment during the preceding weeks of diagnosis of fungal infection.

Concomitant bacterial infections were the following: (1) septicaemia due to *Staphylococcus* in three, *Pseudomonas* and *Acinetobacter* in two each, (2) pulmonary infection with *Legionella* in two and *Klebsiella* and atypical myobacteria in one each, (3) wound infection with *Nocardia asteroides* and *Staphylococcus aureus* in one each. Serology for CMV was positive in 12 (67%). Six (33%) patients were positive for antibodies for hepatitis C virus. Five (28%) patients had insulin requiring diabetes mellitus. Fourteen (78%) patients with systemic fungal infection expired of which four deaths (22%) were attributable to associated fulminant bacterial infections.

Table I. Salient clinical and laboratory features of 18 renal transplant recipients with invasive fungal infection.

Case no.	Name/Age/Sex	Duration after transplant (months)	Type of donor	Duration after rejection	Associated disease/concomitant infection	Immuno-suppression*	Renal function (serum creatinine µmol/l)
1	FS/70,M	4	LURD	3 weeks	Diabetes mellitus, CMV +, Staphylococcal septicaemia	C,P,A	102
2	MK/59,M	36	LURD	No rejection	Diabetes mellitus, CMV +	C,P,A	110
3	HS/59,M	3	LURD	No rejection	CMV +, HBs Ag +, Oral candidiasis	C,P,A	160
4	SR/27,F	3	LURD	1 month	CMV-ND, Staphylococcal septicaemia, Legionella dumoffii infection, Atypical mycobacterium	C,P,A	220
5	HM/45,M	36	LURD	No rejection	CMV-ND, HBs Ag +	C,P,A	108
6	AS/50,M	55	LURD	50 months	Diabetes mellitus, CMV-ND, DIC HBs Ag +, Staphylococcal septicaemia,	C,P	180
7	FM/44,F	48	Cadaver	No rejection	CMV +, HCV +, Klebsiella pneumonia, septicaemia, Staphylococcal abscesses	C,P,A	204
8	WI/55,F	1	First cadaver transplant, 1 month later second LURD transplant	3 weeks	CMV +, HCV +, Hyperthyroidism	C,P,A	550
9	GZ/65,M	1	LURD	2 weeks	CMV −, HCV + Pseudomonas UTI	C,P,A	312
10	SK/59,F	1	LURD	2 weeks	CMV +, Candida UTI	C,P,A	457
11	AS/67,M	1/2	LURD	No rejection	CMV −, HCV +, Candida UTI, Staphylococcal septicaemia	C,P,A	171
12	AR/45,M	23	LURD	No rejection	Diabetes mellitus, CMV +, HCV +, Chronic active hepatitis, Salmonella paratyphi B septicaemia, Herpetic ulcers	C,P	170
13	BA/65,M Kuwaiti	1	LURD	10 days	Steroid induced diabetes mellitus, Leukopenia, Anaemia, Thrombocytopenia	P,A,ALG	700
14	SS/63,F Kuwaiti	108	LRD	No rejection	Diabetes mellitus, Diabetic foot, CMV +; Enterococcus UTI, Pseudomonas septicaemia, Staphylococcal septicaemia, Legionella pneumonia	C,P,A	102
15	AM/34,M	96	LRD	No rejection	CMV +, Malignant lymphoma of ileum & mesenteric lymph nodes, Actineto bacter septicaemia	P,A	108
16	HA/39,F	12	LRD	No rejection	Diabetes mellitus, CMV +, HCV +, Nocardial abscess	C,P,A	120
17	SM/44,M	2	LURD	1 week	CMV +, Leukopenia, Pseudomonas septicaemia	C,P,A	150
18	MM/55,M	1/2	LURD	No rejection	Diabetes mellitus, CMV +, COPD	C,P,A	140

ND, not done; LURD, live unrelated donor; LRD, live related donor; DIC, disseminated intravascular coagulation; HCV, hepatitis C virus.
* Immunosuppression =C, cyclosporine; P, prednisolone; A, azathioprine; ALG, antilymphocyte globulin.

Table II. Roentgenographic features, diagnosis and outcome of 18 renal transplant recipient with invasive fungal infections.

Case no. (as in Table I)	Chest roetgenogram findings	Diagnostic material	Diagnostic evidence	Diagnosis	Treatment	Outcome (Casue of death)
1	Bilateral hazy midzone lesions	Lung biopsy, BAL	Direct microscopy, histopathology	Zygomycosis	AmBisome (2.5g)	Died (Staphylococcal septicaemia)
2	Persistent bilateral pulmonary infiltrates	CSF, blood	C. neoformans in culture, antigen detection	Cryptococcosis	Amphotericin B	Cured
3	Bilateral hazy, diffuse shadows	BAL, blood	C. albicans in culture	Candidiasis	Amphotericin B (1.6g)	Died (Candidiasis)
4	Pneumothorax, bilateral hazy infiltrative and nodular shadows	BAL	A. fumigatus in culture/ direct microscopy	Aspergillosis	Amphotericin B, (3.4g) Rifampicin	Cured
5	Bilateral basal haziness	BAL, bronchoscopic biopsy histopathology	A. fumigatus in culture, direct microscopy	Aspergillosis	Amphotericin B (2.6g)	Cured
6	Normal	Skin biopsy, CSF	C. neoformans in culture, antigen detection	Cryptococcosis	Ampboterei B (2.4g), Fluconozol (8.4g)	Died (Cryptoccocosis)
7	Bilateral midzone and upper zone infiltration	CSF	C. neoformans in culture, antigen detection	Cyptococcosis	Fluconozole (4.8gms)	Died (Cryptoccocosis)
8	Normal	Pus from wound, blood	C. albicans in culture	Candidiasis	Fluconozole (7.2g)	Died (Candidiasis)
9	Normal	Pus from wound, blood resected graft	C. albicans in culture, histopathology	Candidiasis	Amphotericin B (0.750g)	Died (Candidaemia)
10	Normal	Graft biopsy	Direct microscopy, histopathology	Zygomycosis	Amphotericin (1.4g), bladder irrigation	Died (zygomycosis)
11	Bilateral hazy midzone and basal shadows	Blood, urine, sputum	C. albicans in culture	Candidiasis	AmBisome (1.5g), Flagyl	Died (Staphylococcal septicaemia)
12	Rt. sided hazy in filtrative shadows in lower & mid zones	BAL, blood, sputum	C. albicans in culture	Candidiasis	Fluconazole (12.8g)	Recovered, reinfection after 2 yrs, died (Candidiasis)
13	Bilateral hazy diffuse shadow	Necrosed, sloughed wound tissue, nephrectomized graft	A. flavus in culture, histopathology	Aspergillosis	AmBisome (1.8g) Fortom, Amikacin, GM-CSF	Died (Aspergillosis)
14	Bilateral diffuse fluffy shadows	Blood, BAL, urine	C. albicans and T. glabrata (blood) in culture	Candidiasis	AmBisome (2.5g), Fluconazole orally (12g)	Died (pseudomonas and Staphylococcal septicaemia)
15	Normal	Blood, urine	C. albicans in culture	Candidiasis	Amphotericin B (760g)	Died (Candidaemia)
16	Normal	Blood, pus from abscess	C. albicans in culture	Candidiasis	AmBisome (2.1g),	Died (Candidaemia)
17	Bilateral diffuse infiltrative shadows	BAL, bronchial biopsy	A. flavus in culture, direct microscopy	Aspergillosis	AmBisome (3.5g), Rifampicin	Died (Aspergillosis)
18	Normal	Pus, necrosed tissue from the wound	A. fumigatus in culture, direct microscopy	Localised invasive aspergillosis	Amphotericin B-local irrigation	Cured

GM.CSF, Granulocyte–macrophage colony stimulating factor.

Candidiasis

All eight patients with systemic candidiasis presented with fever. Six (75%) patients had concomitant CMV infection. The diagnosis of candidiasis was based on isolation of *Candida albicans* from blood in all cases. In addition, heavy growth of *C. albicans* was recovered from broncho-alveolar lavage, endotracheal secretion and sputum in four, urine and cutaneous abscess in three each and nephrectomy specimen in one patient. *Torulopsis glabrata* was also concomitantly isolated in one case. The mainstay of treatment was parenteral amphotericin B in six (including two with amBisome) and fluconazole in two. Five patients died of severe candidaemia and two from fulminant bacterial septicaemia. The patient who survived the first episode of fungaemia was on treatment with intravenous fluconazole for 32 days and he expired 2 years later due to recurrence of candidiasis.

Cryptococcosis

All three patients presented with fever. One patient had cryptococcal skin abscess alone. Central nervous system manifestations were present in two patients. The diagnosis was established by the isolation of *Cryptococcus neoformans* in culture and by demonstration of cryptococcal antigen in CSF and/or serum. Two patients with meningeal disease also showed the capsulated budding yeast cells in CSF by direct microscopic examination. The patient with skin lesion showed the organism in abscess wall. The earliest incidence of cryptococcal infection after transplantation was 36 months (mean = 46.3 months). Antibodies to hepatitis C was demonstrable in three and CMV in two. One patient each received amphotericin B or fluconazole alone while the third received a combination of both. Both patients with cryptococcal meningitis died.

Aspergillosis

While fever was the commonest presenting symptom in all five patients, pulmonary manifestations were present in four (80%). One patient intially presented with *Aspergillus* skin and graft infection but expired due to respiratory involvement requiring ventilatory assistance. Radiologically, all four subjects had bilateral diffuse infiltrative and fluffy shadows and one was complicated with pneumothorax. One patient had aspergillosis 36 months after transplantation, while the other four had it within 3 months of transplantation. The diagnosis of aspergillosis was established by direct microscopy and culture of the fungus. *Aspergillus fumigatus* was isolated

in three and *A. flavus* in two cases. Among the two patients who were leukopenic, one had CMV disease demonstrated by lung biopsy and serology and the other had *Legionella* pneumonia and atypical mycobacterial infection of the lungs. Two patients received amphotericin B and the other two amBisome. One patient with isolated wound infection was treated with local irrigation of amphotericin B. Two patients received rifampicin along with amphotericin B. Two of the four patients who had extensive pulmonary involvement survived while two patients who had leukopenia in addition expired.

Zygomycosis

Two patients had zygomycosis, one pulmonary and one renal. Pulmonary zygomycosis was diagnosed by demonstrating broad, sparsely septate hyphae in BAL and lung biopsy specimens. This patient died due to fulminant staphylococcal septicaemia and zygomycosis. In the second patient, zygomycotic infection of the allograft was detected on histological examination of the nephrectomized specimen. She died 3 months after transplantation. None had any rhinocerebral manifestations. Both patients had live unrelated donor transplantation and underwent anti-rejection treatment 2–3 weeks prior to the diagnosis of fungal infection. One was treated with amphotericin B and the other with amBisome.

Discussion

Fungi account for 5% of all infections in renal transplant recipients.[2] Even though Rifkind et al.[3] and Gallis et al.[4] earlier reported a high incidence of fungal infection in renal transplant recipients (Table III), the overall incidence is now reported to vary from 0–14%.[5] The 3.5% incidence of fungal infection in the present series is on the lower side in spite of the fact that as many as 48.4% of our transplant recipients have received unrelated donor kidneys and required heavier immunosuppression. It is possible that the diagnosis may have been missed in some because we do not perform diagnostic autopsies.

The incidence of opportunistic fungal infection in renal transplant recipients is largely determined by the interaction between epidemiological exposure and the net state of immunosuppression.[5] High dose immunosuppression, renal functional impairment (66.7%), prior anti-rejection treatment (seven patients) and concurrent viral infections such as CMV (66.7%) and hepatitis viruses (50%) have contributed unfavourably to the net state of immunosuppression in our patients. This would suggest that the immunosuppressed state was primarily responsible for

Table III. Comparative data on systemic fungal infections in renal transplant recipients.

Authors	Rifkind *et al.*[*] (n=51)	Gallis *et al.* (n=171)	Chugh *et al.* (n=310)	Peterson *et al.* (n=535)	Present study (n=512)
Incidence (%)	45	13	6.1	1.3	3.5
Mortality (%)	—	36.4	63	14.3	55.6[†]
Crytpococcosis	—	5.8	2.9	0.2	0.6
Candidiasis	27.4	2.3	2.2	—	1.5
Aspergillosis	13.7	1.2	0.6	0.9	1.0
Zygomycosis	—	1.2	0.6	0.2	0.4
Others	3.9	0.6	—	—	—
Combinations	5.8	2.9	0.3	—	—

[*] This was an autopsy study.
[†] Total mortality was 77.7% while data given here is based on death directly attributed to fungus infection.

fungal infection in our patients more than the environmental factors themselves. It is also relevant that geographically restricted systemic mycoses like histoplasmosis, coccidoidiomycosis and blastomycosis were notably absent in this series.

The reported incidence of *Candida* infection in renal transplant recipients is 3–5%.[4–7] Candidiasis was the commonest fungal infection in our patients but constituted an incidence of only 1.5%. However, all patients had candidaemia. Two patients also had *Candida* pneumonia which is reported to be very rare.[5] One patient also had *Candida* pyelonephritis. A frequent association between candidiasis and CMV infection (75%) was observed in this series. Such an association has been previously reported with *Aspergillus* and *Pneumocystis carinii* infection.[8] Being an endogenous pathogen, *Candida* infections may occur at any time during the post-transplant period but are most frequent during the first 6 months.[9] In the present study, three patients developed systemic candidiasis in the first month after transplantation which is readily explained on heavy immunosuppression for rejection episodes.

Cryptococcal infection rarely occurs during the first 6 months after transplantation.[9] In the present series infection occurred after a mean post-transplant period of 46.3 months which favoured acquired infection rather than reactivation of latent focus. The portal of entry for *Cryptococcus neoformans* is lung from where it haematogenously disseminates particularly to the skin and CNS and less frequently to other sites such as urinary tract and skeletal system.[5] Cryptococcal skin lesion is the first sign of disseminated infection in 30% of patients as was also in our experience.[8] For this reason, early biopsy of an unexplained skin lesion is advised because this may lead to early diagnosis and better chances of recovery.[11] In our hands, the only patient with cryptococcosis who survived had skin abscess. Two patients with meningitis

also had pulmonary lesions and both died. These patients did not have any signs of meningeal irritation and this may be explained on the characteristic absence of exudative inflammation in CNS cryptococcosis.[11]

Invasive aspergillosis is the most important cause of life threatening fungal infection in organ transplant recipients.[12] In more than 90% of cases lungs are the portal of entry for infection although the sinuses and skin damaged by other processes can also be the initial sites of infection.[12–14] Infection due to *A. flavus* in two patients is consistent with local experience. This species has been reported from Sudan and Saudi Arabia as a predominant cause of invasive rhinocerebral disease.[15,16] Four patients (80%) in this study had pulmonary involvement clinically and radiologically while the other single patient had skin wound infection and the organism was isolated from the pus and necrosed tissue. Four patients developed infection during the first 3 months after transplantation. The overall mortality in *Aspergillus* infection has been reported to be as high as 100% and the presence of disseminated disease is closely related to mortality.[12] Those without disseminated disease have a greater than 50% chance of success with appropriate therapy.[12] In the present series, two patients with multisystem involvement expired whereas two with lung involvement and one with skin involvement alone survived. Amphotericin B is still the mainstay in the treatment of aspergillosis. The benefit of concomitant rifampicin administration has been reviewed recently.[12,14]

Zygomycosis is uncommon in renal transplant recipients.[17,18] It produces either a rapidly progressive necrotising pneumonia or rhinocerebral disease.[17] Both our patients did not have rhinocerebral involvement. Diagnosis was reached in one of the patients from a graft biopsy during the first month after transplant; possibly this patient received an infected allograft. This patient expired in spite of amphotericin B administration and in

the absence of any other concomitant infection. The second patient, however, had complicating staphylococcal septicaemia. Both patients had received anti-rejection treatment 2 weeks earlier.

In conclusion, systemic fungal infections continue to be an important cause of morbidity and mortality in transplant recipients. In our hands, this is mainly seen in unrelated donor transplant recipients. The insidious nature of these infections and their protean manifestations delay the diagnosis and institution of appropriate therapy. This along with the unfavourable net state of immunosuppression and concomitant bacterial sepsis contributes to the high mortality in this group of patients. Donor organ transmitted fungus infection could occur in recipients even though it is rare.

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