

## FUNGAL INFECTION IN RENAL ALLOGRAFT RECIPIENTS - AHMEDABAD EXPERIENCE

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### ABBREVIATIONS

CsA : Cyclosporin

CMV : Cytomegalo virus

TIP : Tolerance induction protocol

CSF : Cerebrospinal fluid

HSC : Hematopoietic stem cells

### ABSTRACT

**Introduction :** Transplantation is an acceptable mode of therapy for patients with end stage renal disease. Immunosuppression makes these patients vulnerable to infection and other complications.

**Material and Methods :** We carried out a retrospective study of fungal infections in renal allograft recipients at our institute, from Jan 1<sup>st</sup> 2002 to July 31<sup>st</sup> 2005 in 513 patients. The common sites of infections were urinary tract, surgical incision and lungs. Cumulative incidence of mycotic infection, time of occurrence and outcome were recorded and analyzed.

**Results :** Out of 513 patients, 24 (4.67 %) were found to have fungal infections. The average time of occurrence was 143 days post-transplant. Fungal genera noted were *C. albicans* in 21 (87.5 %), *Cryptococcus neoformans* in 1 (4.16 %) and zygomycosis in 2 (8.34 %) patients. All of them were receiving Cyclosporine,  $3 \pm 1$  mg/ kgBW/day, Prednisolone, 10 mg/day, and 3 patients were also taking Mycophenolate mofetil, 1 gm/day.

**Conclusion :** The overall incidence of fungal infections in our center was 4.67 % and predominant fungal infection was *Candida albicans*. Significantly better recovery may be attributed to low dose of immunosuppression accompanied by early diagnosis and aggressive management.

### INTRODUCTION

Transplantation is an acceptable mode of therapy for patients with end stage renal disease. Infections account for significant morbidity and mortality among renal transplant patients, particularly in the tropics<sup>1,2</sup>. Immunosuppressive therapy, prolonged antibiotic administration, leucopenia,

malnutrition, diabetes mellitus and uremia predispose these patients to mycotic infections. In addition, hot climate, high humidity, low socioeconomic status, clothing habits and poor personal hygiene are contributing factors. Other risk factors are cytomegalo virus (CMV) infection and chronic liver diseases in these set of patients.

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## MATERIAL AND METHODS

We carried out a retrospective study of fungal infections in renal allograft recipients at the Institute of Kidney Diseases and Research Centre and Institute of Transplantation Sciences, Ahmedabad, from Jan 1<sup>st</sup> 2002 to July 31<sup>st</sup> 2005 in 513 patients who underwent renal transplantation in this period. Out of these patients, 329 underwent renal transplantation under tolerance induction protocol (TIP) and 184 opted for transplantation without tolerance induction protocol.

The TIP included 2 leucocyte infusions from donor to recipient followed by target specific low dose fractionated irradiation (500 cGy x 4 alternate days) to sub-diaphragmatic lymph nodes, spleen, vertebral bodies and part of pelvic bones; conditioning with Cyclosporine (CsA), 3 mg/kg BW/day, and simultaneous non-myeloablative low intensity conditioning was done with cyclophosphamide, 10 mg/kg BW/day, polyclonal anti-rabbit T-cell antibody, 1.5 mg/Kg BW and Treosulphan, 15 ng / Kg BW each, in a single dose. High dose hematopoietic stem cell (HSC) administration in unmodified form with target of =  $20 \times 10^8$  nucleated cells / kg BW was performed subsequently. This was administered in thymus, marrow, portal and peripheral circulation.

The second group of patients was transplanted directly. Both groups were followed up at the same outpatient clinic at the same time intervals where the same clinico-lab parameters were monitored.

The most common sites of infections were urinary tract, surgical incision, and lungs. Cumulative incidence of mycotic infection, time of occurrence and outcome were recorded and analyzed.

After clinical work-up the samples from suspected infection sites were collected. These samples included urine, throat swab, wound swab, broncho-alveolar lavage, blood cultures, cerebro-spinal fluid (CSF), DJ stents and tissue biopsies. Gram stain and India ink preparation in CSF samples were performed and recorded. The samples were then subjected to culture in incubators/ Bactec using blood agar, McConkey agar, and Sabaroud's agar for fungal culture. In Sabaroud's medium the tubes were checked every day till 21 days before reporting them as negative. Positive cultures were recorded for their colony characters and Gram stained to define the type of fungi. They were then subjected to sensitivity using standard anti-fungal drugs which included Amphotericin, Flucunazole, Nystatin, Clotrimoxazol, Ketoconazole and Itraconazole.

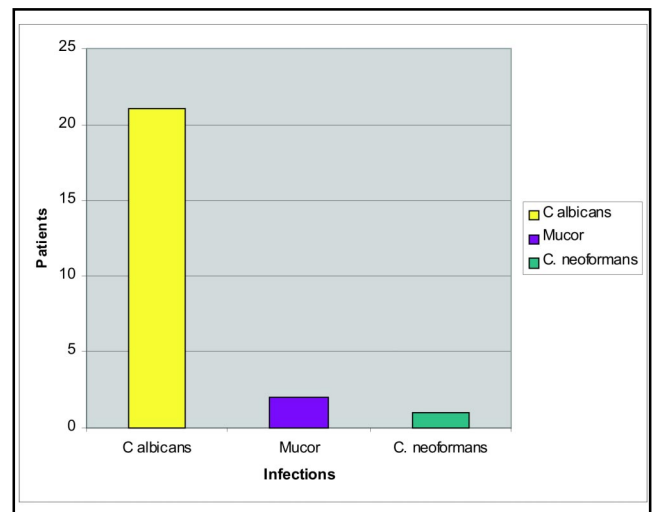
Tissue biopsies were processed in Leica tissue processor TP 1010 and cut in tissue microtome at 4  $\mu$ m. They were then

stained using Harris' hematoxylin, Periodic acid Schiff and silver methanamine stains for microscopic examination.

Patients with cryptococcal infection presented with features of meningitis and the diagnosis was confirmed using India ink preparation. Patients with mucor mycosis had peri-orbital cellulitis and black necrotic pus discharging from nasal mucosa and palate that characteristically showed mucor when mucosal tissue was examined. Local candidiasis affecting urinary tract presented with features of pyelonephritis affecting the graft and was confirmed with culture.

Follow up samples were again cultured to look for response to the anti-fungal treatment and correlated with clinical response.

## RESULTS



**Figure 1** Different fungal infections noted in renal allograft recipients

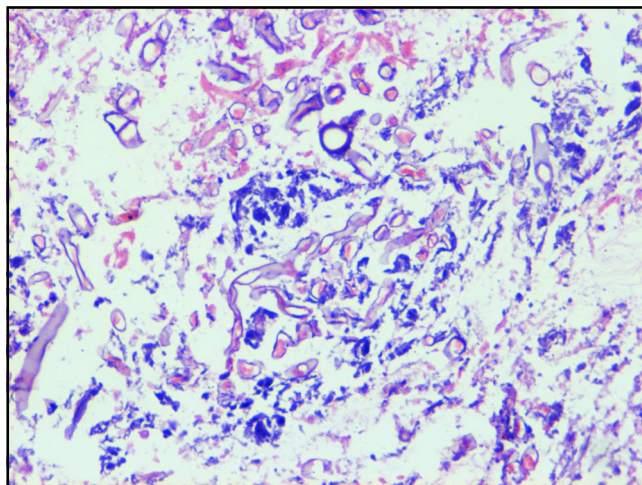
H & E stain, x 100

Out of 513 patients, 24 (4.67 %) were found to have fungal infections. The average time of occurrence was 143 days post-transplant. The average time of diagnosis after clinical suspicion was 1 day (ranging from 6 hours to 46 hours). The fungal genera noted were *C. albicans* in 21 (87.5 %), *Cryptococcus neoformans* in 1 (4.16 %) and zygomycosis in 2 (8.34 %) patients (figure 1). Four (16.66 %) patients out of 24 died; two patients had zygomycosis and remaining two had *C. albicans* with CMV infection.

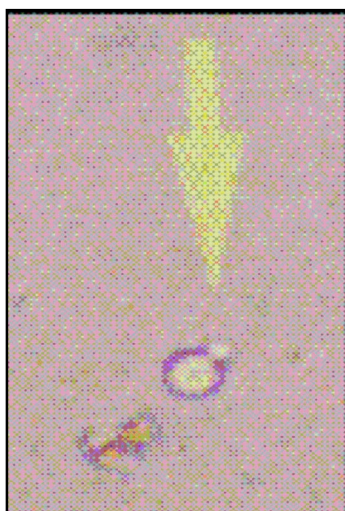
All patients were receiving CsA,  $3 \pm 1$  mg/kg BW/day, Prednisolone, 10 mg/ day and 3 patients were taking mycophenolate (MMF), 1 gm/day.

*C. albicans* was present in 6 urine samples, 4 stool samples, 4 throat swabs, 2 DJ tips, 1 broncho-alveolar lavage and 4 drain fluids.

Mucor was found in 1 pus sample from surgical wound site and 2 tissue biopsies, 1 each from nasal sinus and palate (figure 2,3). Cryptococcus was found in 1 CSF sample.



**Figure 2** Empty looking aseptate fungal hyphae (of mucor) in necrotic and hemorrhagic background.



**Figure 3** India Ink preparation Demonstrating Capsule and Bud forms of Cryptococcus Neoformans.

## DISCUSSION

Opportunistic fungal infections are an important complication in renal transplant recipients in India where an estimated 4,000 renal transplants are performed annually with varying immunosuppressive protocols<sup>3</sup>. The prevalence of local

mycosis of 4.67 % in our study is lesser as compared to study from southern India which has reported an incidence of 6.6 % systemic mycoses<sup>4</sup>. In western countries the prevalence ranges from 1.4 % to 9.4 %<sup>5,6</sup>. In US, 66 % fungal infections occurred after 6 months post-transplant and 22 % were reported after 2 months posttransplant<sup>7</sup>. All these patients were on standard triple drug immunosuppression. In our study, most of the patients had fungal infections within 6 months posttransplant. This may be due to high ambient fungal load in the overcrowded and humid environment. Systemic mycosis described in 18 renal transplant recipients from India more than a decade ago had reported mortality of 66 %<sup>8</sup>. In our study with no systemic mycoses, mortality was noted in 16.7 % patients. This reflects very good patient care and better anti-fungal management in presence of tolerance induction protocol where the immune status of patients is well preserved as compared to standard transplantation medicine practiced all over the world.

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