

# Cytological Diagnosis of Infections in Renal Allograft Recipients

Radha S\*, Tameem A\*, Fernandez DK<sup>†</sup>

## Abstract

*Infection is the most common cause of mortality and morbidity within the first year of transplantation. Renal allograft recipients are susceptible to various opportunistic infections because of prolonged immunosuppression. The study was carried out to evaluate the role of cytology for rapid diagnosis of infections in transplant patients. Fine needle aspiration cytology (FNAC) of superficial lesions, guided aspirations from deep seated lesions, bronchoalveolar lavage, endoscopic brushings and urine cytology was the material studied. 292 renal transplants were done during a period of nine years. 46 cases of infections were diagnosed, comprising of bacterial (26), viral (2), fungal (13) and mixed bacterial and fungal (5). Cytological examination offers a rapid and specific diagnosis of infections in these immunocompromised patients. The incidence, severity of infection and mortality in post transplant patients will decrease with early diagnosis and high index of clinical suspicion.*

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**Key Words:** Post transplant infections, cytological diagnosis.

## Introduction

Infections occurring after transplantation account for half of the deaths in post transplant patients. During the first post transplantation year, 40-50% of recipients experience atleast one infection. The incidence of infection is directly related to the net immunosuppressive effect achieved. Infections most commonly occur in mucocutaneous areas (41%), urinary tract (17.2%) and respiratory tract (13.9%). The common infective agents are bacterial, viral, fungal and protozoal. In the first month infections are directly related to surgery, the next six months are associated with high levels of immunosuppression and carry a risk for opportunistic infections. Early diagnosis and prolonged treatment are required for eradication of these infectious agents. Cytological material can provide a rapid, sensitive and specific diagnosis of infections. It also provides material for ancillary studies. Fine needle aspiration cytology (FNAC) has been reported to be a highly sensitive and specific diagnostic tool in the management of

post-transplant patients.<sup>1</sup> When correctly used, bronchoalveolar lavage too is a safe and useful procedure with a high diagnostic yield in immunocompromised host.<sup>2</sup>

## Materials and Methods

This study was done in department of pathology over a period of nine years (1997-2005). During this period 292 renal transplants were done from live related donors and cadavers. Immunosuppression was induced with three doses of methyl prednisolone followed by tapering doses over three months. They were maintained on cyclosporine and azathioprine. High risk transplants recipients were induced with basiliximab. All the transplant recipients received antiviral prophylaxis with acyclovir from day one of transplant for three months and antifungal prophylaxis with flucanazole for two months. FNAC of superficial lesions, guided aspirations from deep seated lesions, bronchoalveolar lavage (BAL), endoscopic brushings and urine cytology was the material studied. Smears were stained with

<sup>†</sup>Consultant Pathologists, \*Consultant Nephrologist; Kamineni Hospitals, L.B. Nagar, Hyderabad.

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**Corresponding Author:** Dr. S. Radha, Plot No.:20, Road No.:1, Alakapuri, Hyderabad - 500035, Andhra Pradesh.

**E-mail:** sradha\_21@hotmail.com

Haematoxylin and Eosin (H&E). Stains for acid fast bacilli (AFB) and fungus were done for all the cases.

### Observations

We diagnosed forty six cases of infections on cytology. Male to female ratio was 2.8:1 and age of the patients ranged from 21 to 69 years. Pulmonary infections were the commonest infections in our series. Commonest presentation was fever with respiratory symptoms. Skin lesions varied from single to multiple cutaneous abscesses. Basic cytological inflammatory responses like acute inflammation, chronic inflammation, granulomatous inflammation and necrosis were observed. Tissue response in lesions diagnosed and confirmed with Ziehl Neelsen stain as tuberculous lesions was both acute inflammatory and granulomatous.

Candidiasis was diagnosed based on the presence of small elliptical yeast and pseudohyphae. The lesions diagnosed as zygomycetes had broad sparsely septate hyphae that branched haphazardly. Aspergillus lesions revealed thin regular hyphae which were septate and branched at acute angles. The morphology of all the fungal lesions was confirmed on silver stains.

The tissue response in the single case of

cytomegalovirus (CMV) was mononuclear infiltration; infected cells were enlarged with a large basophilic intranuclear inclusion. Decoy cells in BK virus nephropathy revealed an enlarged nucleus with a smudged basophilic appearance. The lesions of Pneumocystis revealed foamy exudates on H&E and the helmet shaped cysts were seen on silver stains. Nocardial lesions revealed thin branching irregular bacilli on silver stains and these were weakly AFB positive. Clinical and cytological details are given in Table 1.

### Discussion

Major complication of renal transplant recipients is infection. During the first post transplant year 40%-50% of transplant recipients experience at least one infection. Multiple factors including tropical climate, diabetes, chronic hepatitis and late presentation contribute to poor outcome. The time table for occurrence of infections is shown in Table 2.<sup>3</sup>

In our study bacterial infections occurred within the first two weeks of transplantation. Nocardial lesions occurred two months to one year and viral infections occurred two years after transplantation. Fungal infections occurred from six month to three

**Table 1 : Post transplant infections-clinicopathological findings**

Infectious agent	Number	Site	Material studied	Response to treatment
<b>Bacterial Infections</b>				
Mycobacterial infections	16	Lung-15 Lymph node-1	BAL-10FNAC-6	Recovered-10 Expired-5 Lost to follow up-1
Nocardia	5	Skin-1 Lung-4	FNAC-1 BAL-4	Recovered-1 Expired-4
Nonspecific infections	5	Lung abscess-2 Perinephric abscess-2 Skin abscess-1	FNAC FNAC FNAC	Recovered-5
<b>Viral Infections</b>				
Cytomegalovirus	1	Lung-1	Brush Cytology	Expired
Polyoma virus	1	Graft-1	Urine Cytology	Graft loss
<b>Fungal Infections</b>				
Candida	3	Lung-2 Skin-1	BAL-2 FNAC-1	Recovered-3
Aspergillus	6	Lung-5 Skin-1	BAL-2, FNAC-3 FNAC-1	Recovered-2 Expired-3 Recovered-1
Zygomycosis	3	Lung-3	BAL-1 FNAC-2	Expired-3
Pneumocystis	1	Lung-1	BAL-1	Expired-1
<b>Combined Infections</b>				
Candida with AFB	1	Lung	FNAC	Recovered
Nocardia with AFB	2	Lung	BAL-2	Recovered-2
Aspergillus with AFB	1	Lung	FNAC	Expired
Candida+Aspergillus+AFB	1	Lung	FNAC	Expired

**Table 2 : Time table for occurrence of infections<sup>3</sup>**

0-1 month Conventional Nosocomial infections	1-6 months Unconventional or Opportunistic infections	After 6 months Community acquired or persistent infections
Bacterial infections of lung, urinary tract	Cytomegalovirus Ebstein Barr virus Herpes simplex virus	Cytomegalovirus Human papilloma virus
Candidiasis	Hepatitis B & C virus	Cryptococcus
Herpes simplex virus	Aspergillus Pneumocystis carinii Candidiasis Mycobacterial Endemic fungi Nocardia Parasitic infections	Hepatitis B & C Mycobacterial Aspergillus Endemic Fungi

years. Of solid organ transplants, renal transplant is associated with lowest rates of infection. This is because renal transplant is an elective or semi elective procedure.<sup>4</sup> In our study 46 patients developed infections out of 292 transplants. Out of the five nonspecific bacterial infections, two patients had perirenal abscesses and two had lower respiratory tract infections and one patient had a cutaneous abscess.

Sixteen patients had mycobacterial infections. Fifteen lung lesions and one lymphnodal lesion were diagnosed as mycobacteriosis (Fig. 1). Five patients had other associated infections. AFB was demonstrated in all the cases and culture was done in two cases. Both the cultures yielded *Mycobacterium tuberculosis*. The incidence of tuberculosis in post transplant cases is 10-15% as against 1-2% in general population.<sup>5</sup> The mortality in post transplant patients from tuberculosis is 10.5-23%. In our study all the ten patients with isolated tuberculous lesions recovered with initiation of anti tuberculous therapy. Five patients with combined infections expired. One patient was lost to follow up. Mortality correlates with the duration of symptoms prior to antituberculous treatment, and therefore early recognition and treatment is essential as the course of the disease can be rapidly fatal in tuberculosis.<sup>6</sup>

Twelve cases had fungal infections and in five cases, it was associated with other infections. Ten lesions were from lung and two were from cutaneous abscesses. The species identified were aspergillosis, zygomycosis and candidiasis. One patient was diagnosed on BAL to have pneumocystis. The incidence of fungal infections in live renal transplant recipients is 6.1%.<sup>7</sup> Candidiasis and aspergillosis were

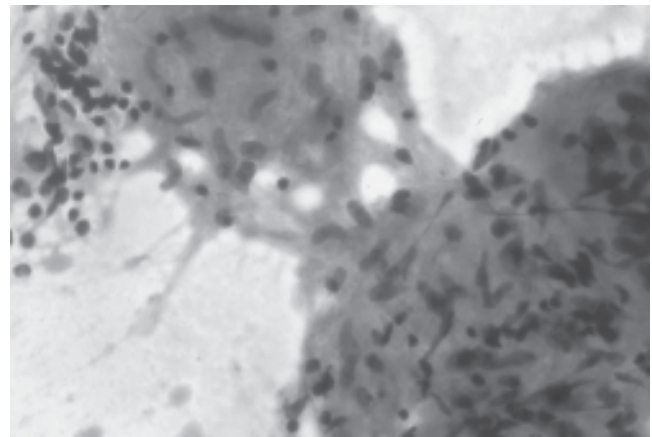


Fig.1 : Epithelioid cell granuloma with giant cell (H&amp;E, x 400).

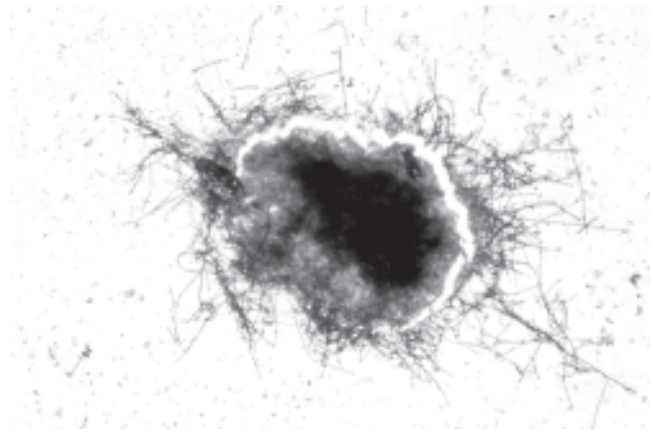


Fig. 2 : Nocardial abscess (Silver Methenamine, x 100).

common infections as was reported by other workers.<sup>8</sup> The risk factors for fungal infections are multifactorial. In our patients risk factors included immunosuppressive therapy and diabetes mellitus. The mortality due to fungal infections is 65%.<sup>9</sup> The mortality in our series was 50%. The outcome of fungal infections may improve with high index of clinical suspicion, early diagnosis and appropriate treatment.

Five patients had nocardial abscesses, four were from the lung and one was a cutaneous abscess (Fig. 2). Among renal transplants recipients nocardiosis is a marker of high susceptibility to tuberculosis and other infections. The association with tuberculosis is high in patients if the infections develop within two years of transplant.<sup>10</sup> In two of our cases there was associated tuberculosis.

Two patients were diagnosed to have viral infections, one was *cytomegalovirus* which was diagnosed on endoscopic brush cytology and the other was *polyoma virus*. The latter was suspected on urine cytology and was confirmed on a graft biopsy. The prevalence of CMV in transplant patients is

21.8%.<sup>11</sup> Infection in our patient had a relationship with an acute rejection episode. Sakhuja et al<sup>11</sup> had documented CMV in 12 of the 69 autopsies between 1992-1997. In our study only one case of CMV was diagnosed on cytology and the rest were diagnosed on biopsies. Urine cytology of one patient with deteriorating graft function revealed decoy cells and his graft biopsy revealed features of polyoma virus nephropathy. BK virus associated interstitial nephritis is a significant cause of allograft dysfunction in 2-5% of patients. The disorder has poor prognosis and approximately 50% of allografts failing over subsequent months.<sup>12</sup>

To conclude, infections remain the major hazard of transplantation in India. The incidence, severity of infection and mortality in post transplant patients will decrease with early diagnosis and high index of clinical suspicion. Different cytological techniques play an important role in achieving this goal.

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