CHEST INFECTION IN KIDNEY GRAFT RECIPIENTS

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ABSTRACT

Objective: To estimate the incidence of chest infections in renal allograft recipients, the mortality of lung infections, the incidence of Tuberculosis, its common presenting features, and determine significant risk factors for such infections.

Methods: Over an eighteen month period (January 2001 to July 2002), 100 kidney graft recipients were checked for any past or present history of chest infection. All the recipients acquired their graft from living related or unrelated donors. The study was conducted in Al-Shaheed Adnan Hospital Centre for kidney disease and transplantations in Medical city, Baghdad Teaching Hospital and Al-Karama Teaching Hospital. Statistical analyses were carried out using Chi square test and Yate's correction wherever needed. A P value of less than 0.05 was taken as significant.

Results: Bacterial pneumonia was the commonest pulmonary infection (n=13, 32.5%) followed by the probable acute viral bronchitis (n=10, 25%), pulmonary tuberculosis (n=9, 22.5%) and fungal infection in five (n=5, 12.5%), nocardiosis in two and candidacies in three recipients. The mortality from chest infections including pulmonary tuberculosis in renal allograft recipients was seven (17.5%) recipients.

Conclusion: Pulmonary tuberculosis should be included in the differential diagnosis of infections causing fever of unknown origin in the renal transplant patients, especially in endemic areas. Leucopenia and diabetes mellitus were significant risk factors for serious pulmonary infections. Unrelated donor is also a risk factor for serious post renal transplant recipient pulmonary infections including tuberculosis which presents with high grade intermittent fever.

Key words: Chest infections, Renal transplant, Tuberculosis

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Introduction

Bacterial infections usually occur in the first month following transplantation, and technical issues related to the procedure can play an important etiological role.[1] Pulmonary infections were less common in patients treated with cyclosporine (CsA) compared to those receiving Azathioprine (probably due to the fact, that Azathioprine may cause leukocytopenia).[2,3] However, there seems to be an increased risk in patients treated with anti-lymphocyte globulin (ALG) or monoclonal antibody (OKT3) for acute rejection[4] or in the course of induction therapy.[5,6] Some studies[4,7,8] could demonstrate more frequent pulmonary infections when the monoclonal antibody (OKT3) was used.

Currently the use of cyclosporine A (CsA) combined with low dose steroids has resulted in decrease in the incidence of post renal transplant opportunistic infection.[9,10]

Beyond six months, in patients with well functioning allograft who are on stable maintenance immunosuppressant the pattern of infection is similar to that in the general population.[11-13] In general, during the first postoperative months, bacterial pneumonias predominate. Two to four

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months after transplantation, pneumonia is caused by both opportunistic and bacterial pathogens. Patients with stable graft function on minimal immunosuppression beyond one year contract primarily bacterial pneumonia.[13-15] However, the time table of infection in tropics may be some what different with sixth month milestone not demarcating the risk of the opportunistic versus conventional infection[16] (Table I).

Mycobacterial disease should be considered in any patient with fever of unknown aetiology[17] and positive tuberculin test is included in the risk factors for reactivation of tuberculosis in renal allograft recipient.[18] Mycobacterial infection, although suggested by many to be common in haemodialysis patients has seldom been reported in the literature prior to 1996 and most reports have described a small number of cases.[19,20] In the past two years five reports have emerged from developing countries suggesting either a resurgence or greater recognition of this infection.[21,22] Since the prevalence of tuberculosis in end stage renal disease and kidney graft recipients patients is high in developing countries, the insight gained into the diagnosis and treatment of Mycobacterium tuberculosis, in these patients will be of value to nephrologists.[23,24]

Method

Over an eighteen months period (January 2001 to July 2002), 100 kidney graft recipients were checked for any past or present history of chest infection. All the recipients had their graft from living related or unrelated donors.

The study was conducted prospectively and retrospectively in Al-Shaheed Adnan Hospital Centre for kidney disease and transplantations in Medical city, Baghdad Teaching Hospital and Al-Karama Teaching Hospital. Triple immuno-suppresion drug therapy (Cyclosporine A, Azathioprine and Steroid) was given to all the kidney graft recipients during the induction of immunosuppression and sometimes during the maintenance phases.

Data of chest infection were taken from patients' files for those patients who were checked retrospectively. The patients' ages ranged 14-65 years. Among the patients who were studied 40 had chest infection and among the latter nine had pulmonary tuberculosis.

Twenty six patients were male and 14 were female. The data were obtained from patients during their routine follow up.

Most of those patients with pulmonary infection had a serious systemic infection and stayed in the intensive care unit of renal transplant for several days or weeks. All such patients underwent septic work up for infections in the post transplant period-namely blood, urine and sputum cultures for bacteria, Fungi and mycobacterium (Acid fast bacilli). Four patients underwent fiberoptic bronchoscopy for bronchial washing/brushing for culture.

Laboratory work up for pulmonary tuberculosis such as sputum or bronchoalveolar lavage for acid fast bacillus, tuberculin skin testing were done When initial work up was negative and the problem persisted despite three days of hospitalization with definitive radiological findings persisting and in cases where presumptive diagnosis of tuberculosis was made. Pleural fluid aspiration and pleural biopsy were done when considered appropriate. The follow up ranged from three days to seven weeks with a mean of 32 days (median 28 days). Diagnosis of pulmonary infection in certain instances (three patients) was based on therapeutic Trial (Anti -TB) where investigations failed to reveal basic microbiological diagnosis. Leucopoenia was treated with Azathioprine withdrawal, blood transfusion and changing the dose of steroid in appropriate cases. Some results of analysis are expressed as mean ±SD (Standard Deviation) and compared with Mobia Indian and Hyderabad (HS) studies. Statistical analysis was carried out using Chi square test and Yate's correction wherever needed. A P value of less than 0.05 was taken as significant.

Results

Of the 100 patients who were studied, 40 patients developed pulmonary infection. Five patients with fungal infection (12.5%) (nocardiosis in two and candidiasis in three) as proved by sputum culture were leucopenic and the patient with Cytomegalovirus (CMV) as (proved by seroconversion) also was leucopenic. Nine patients had Pulmonary Tuberculosis and two thirds of them (n=6, 66.6%) had their graft from unrelated donors.

We found that patients who have Diabetes Mellitus and leucopenia were at a high risk of getting post transplant pulmonary infection (Table II).

Table I. The characteristics of post transplant chest infections

Infectious disease of the chest	Sex		Duration of Renal Transplant		Donor/recipient relationship	
	m	f	<3m/y	>3m/y	R.D	UR.D
1. Pneumonia	6	7	3	10	4	9
2. TB	8	1	2	7	3	6
3. Fungal infection	3	2	2	3	1	4
4. Pneumocystic carini pneumonia	2	0	2	0	1	1
5. CMV	0	1	0	1	0	1
6. Acute bronchitis (viral)	7	3	8	2	0	10

Table II. Risk factors for post-transplant serious infections

Renal transplant Pt.	Total	Sex	Diabetes	Leucopenia <4000/cmL	Renal dysfunction CS.cr.>1.1	Age>40yr.
Hyderabad study (HS)	142	Male=97 Female=45	44(32.8%)	18(12.22%)	43(28.16%)	59(41.5%)
Baghdad study (BS)	100	Male=52 Female=48	32(32%)	56(56%)	60(60%)	10(10%)
Pulmonary inf. HS	27	Male=16 Female=11	12(44.4%)	8(29.6%)*	11(40.01%)	15(55.5%)
Pulmonary inf. BS	40	Male=26 Female=14	20(50%)	10(25%)**	28(70%)	5(12.5%)
Pulmonary inf. Related deaths in HS	11	Male=5 Female=6	4(36.36%)	3(27.27%)	4(36.36%)	2(18.1%)
Pulmonary inf. Related deaths in BS	7	Male=4 Female=3	4(57.1%)	5(71.4%)	3(42.8%)	2(28.56%)
		P=0.057	*P*=0.03	*P*= 0.0001	*P*=0.14	*P*=0.73

Significant on Chi-square test analysis

* Hyderabad study (HS) = P< 0.001 **Baghdad study (BS) = P<0.000

Table III demonstrates the demographics of our patients. Forty patients (26 males, 14 females) were diagnosed as having post transplant chest infection which is compared with the result of the Mutubia study held in Pakistan. The mean age of our renal transplant patients was 25.2±6.6 (14-65) years. The prevalence of Tuberculosis in our patients was 9/40 (22.5%). The onset of the symptoms was 3-24 (10.2±6.6) months after renal transplantation.

Table IV show the features consistent with pneumonitis (cough, sputum, fever, fine crackles, radiological opacity or dyspnoea) necessitating hospitalization were observed in two patients among those having tuberculosis (TB). While some of these clinical features were seen in the remaining seven patients: two third had anorexia, nausea and fever, one third had dry cough and fever, and pleuritic chest pain.

Table V shows the results according to the investigation that were done to our patients compared with those in the Mobia Indian study (MS). Pleural effusion was seen in 4/9 of our patients with TB and pulmonary infiltrate was seen in 5/9 patients. Positive sputum for Acid Fast Bacillus (AFB) was seen in only one of our patients Exudative pleural fluid was seen in three out of four (75%) of our patients.

Discussion

In our study, bacterial pneumonia was the commonest pulmonary infection (n=13, 32.5%) followed by the probable acute viral bronchitis (n=10/40, 25%), pulmonary tuberculosis (n=9, 22.5%) and fungal infection (n=5, 12.5%) (Nocardiosis in two and candidiasis in three).

Pneumocytis carinii pneumonia (PCP) was diagnosed on clinical bases and response to treatment, because of shortage of diagnostic tests. Though the clinical findings were not of any diagnostic value per se, the combination of respiratory failure with interstitial shadowing and few auscultatory lung signs, which are characteristically due to PCP, were seen only in two patients in our series with gratifying outcome.

Candida and nocardiasis were the cause of pulmonary infection in five patients (12.5%) and they were the commonest fungal infection in this study. These findings were comparable to other studies.[25] A previous study in Iraq by Dr. Ibrahim, summarized that nocardia asteroids and Candida albicans were the major opportunistic pathogen for development of pulmonary infection in renal transplant patients.[26]

Cytomegalovirus (CMV) disease was quite uncommon and because of the lack of diagnostic

Table III. Demographic characteristic of patients with pulmonary tuberculosis in renal transplantation (compared with Mutubai Pakistan study)

Number	Mutubai study	BS
1. Total No.	109	40
2. Patient with TB	16(14.6%)	9(22.2%)
3. Age years mean ± SD	33.4 ± 11.9	25.2±6.6
4. Sex ratio M:F	3:1	2:1
5. Time of RT (in months) when TB detected	6.5 ± 4.8 (1-18)	10.2±6.6 (3-24)

Table IV. Clinical symptoms of pulmonary tuberculosis in renal transplant patients

RT	Number	%
1. Loss of appetite / nausea	6	60.5
2. Fever persistent low grade / high intermittent	3 and 5	33.3 and 55
3. Dry cough	3	33
4. Pleural pain	2	22

Table V. Diagnostic procedures performed in pulmonary tuberculosis patients after renal transplantation (compared with Mobia study)

Diagnostic procedures	M.S N=16	B.S N=9
1. CXR: Plural effusion Pulmonary infiltration	3(18.7%) 4(25%)	4(44.4%) 5(55.5%)
2. Suptum for AFB	3(18.7%)	1(11.1%)
3. Pleural fluid analysis: exudative transudative	3/3(100%) 0(0%)	3/4(75%) 1/4(25%)
4. pleural biopsy	3/4(75%)	2/4(50%)
5. Bronchial lavage smear for AFB	1/1(100%)	2/4(50%)

facilities it was suspected in one patient but the diagnosis could not be established other than that positive high titers of IgM antibody to CMV were detected in this patient.

The table also shows that those patients who received their grafts from unrelated donors, developed post RT pulmonary TB in a higher percentage (n=6, 66.6%), probably these recipients are more liable for graft rejection and therefore needed higher doses of immunosuppressive therapy.

Table II shows that recipients who are at increased risk for infection include those who have leucopenia and diabetes mellitus.

In our series of lung infection, leucopoenia was present in 56/100 (56%) and 10/40 (25%) of leucopenics had serious pulmonary infection, among those with serious pulmonary infections 7/10 (70%) has significant leucopoenia with WBCs<1000 c/ml.

Patients with leucopoenia at an early stage may have asymptomatic lung infection, they necessitate periodic radiological screening, and early diagnosis has gratifying outcomes. Though diabetes was found to be significant risk factor for serious post transplant pulmonary infections (P<0.03) it was comparable with others,[27] however leucopoenia was found to be a significant risk factor for all kinds of serious infections including pulmonary ones (P<0.0001).

As compared with the Hyderabad study which concluded that age, gender, diabetes, and impaired renal functions, are not significant risk factors for post transplant infection, we found in our study that diabetes mellitus and leucopenia were significant risk factors for post transplant infections.

As the outcome is related to precise diagnosis, the diagnostic material for cytological study and culture are important.[28] The specimens for diagnostic work up are sputum, bronchoalveolar lavage, pleural fluid aspirate in addition to blood culture and serodiagnosis. The order of such sample analysis depends upon the case, diagnostic set up, time of presentation, and initial work up results. In most of our cases, patients received broad spectrum antibiotics from the first day and depending upon the initial work up, treatment that begun was either continued (in case of improvement) or changed In case of no improvement with negative microbiological reports, patients were given a trial of antituberculous drugs and/or antifungal therapy based on presumptive possible diagnosis.

Seven out of the 40 patients died (17.5%) and the causes were as the follows; lung abscess in two patients (28.75%), undiagnosed in four patient (57.1%) and disseminated tuberculosis in one patient (14.2%). Out of the deaths, four patients died within three weeks of hospitalization. The cause of

death could be attributed to delay in treatment in four patients one of them is the patient who died with disseminated TB.

In this study, pulmonary infection continues to be a common complication of immunosuppression (n=40, 40%) with high mortality (n=7, 17.2%). Increased awareness and aggressive approach is required to prevent such fatalities. Renal dysfunction (n=28, 70%) as well as age and gender were not the major factors in deciding the outcome in pulmonary infection. Leucopenia (n=10, 25%) and diabetes mellitus (n=20, 50%), with P values of P=0.0001 and 0.03 respectively, were significant risk factors for all serious pulmonary infection. Diagnostic problem with delay in appropriate therapy was a significant predictive factor of death and fatalities were high in chest infection occurring within the first six months.

The present study underlines the role of infections in the morbidity and mortality in renal transplant recipients and highlights the risk of nosocomial exposure hazards if corrective steps are not undertaken. The hazards of leucopenia, diabetic host and immunomodulating viruses also look important in this analysis of causation and mortality of pulmonary infection. The high incidence of post transplant pulmonary TB in our study is similar to that reported from other centres in developing countries.[29]

In Iraq and India the prevalence of TB in the general population is 20-25 times higher than in developed countries and it is 7-8 times higher in end stage renal disease (ESRD) patients compared to the general population.[29] In this study the prevalence of TB in renal transplant patient is 9/40 (22.2%) which is comparable to findings in other developing countries such as India and Pakistan[30] and Turkey.[31]

Table III compares the demographic characteristics of patients with post transplant pulmonary TB in our study with that in the Mutubai study in Pakistan which shows that the onset of post transplant pulmonary infections occur later (10.2±6.6 compared 6.5±4.8 months) which may be due to that the patients become more exposed to the sources of infections as they come more in contact with the community.

The most common presenting signs of TB in renal transplant patients in this study (Table IV) were fever and weight loss. High grade intermittent fever was most common in renal transplant patients in our study (55%), and in (68%) of renal transplant patients with TB in Pakistan by Naqvi *et al.*[32] and in 63% of patients in India by Sakhuja *et al.*[33] In renal transplant patients TB could easily be mistaken for other common infections, such as Cytomegalovirus (CMV), that can present with intermittent spiking fever. Further, fever of unknown origin was seen, only in renal transplant patients necessitating empiric anti TB therapy.[32,33]

There were nine patients with TB who had invasive and non invasive investigations. Six of such patients were diagnosed based on: direct sputum exam in one patient (1/9, 11.1%), bronchoalveolar lavage in two patients (2/4, 50%), pleural fluid analysis in one patient (1/4, 25%), histological diagnosis of pleural biopsy in two patients (2/4, 50%) and therapeutic response to anti TB trial in three patients (3/9, 33.3%). The mortality in such group was one who had disseminated TB out of nine patients with TB (11.1%) (Table V).

Our results were comparable with those of the Mobia Indian study; both revealed that the sputum yield is less positively for acid fast bacillus (AFB) in patients on immunosuppression therapy (1/9, 11.1%) compared with the Mobia study (3/16, 18.7%).

Pulmonary TB was the most common form of the disease in renal transplant patients. It presented as either infiltrates or effusions,[34,35] our results are comparable with those of others.

Whether post transplant pulmonary tuberculosis is a reactivation or new infection in our patients is unknown. The recent molecular epidemiology techniques have shown that reinfection rather than reactivation of TB occur in immune comprised hosts.[35]

Conclusions

Bacterial pneumonia is the commonest pulmonary infection (13/40, 32.5%) followed by the probable acute viral bronchitis (10/40, 25%), pulmonary tuberculosis (9/40, 22.2%) and fungal infection in five (5/40, 12.5%) with Nocardiosis in two patients and candidiasis in three.

Tuberculosis presents with high grade intermittent fever in renal transplant patients. Tuberculosis should be included in the differential diagnosis of infections causing fever of unknown origin in the kidney graft recipients, especially in endemic areas.

Leucopenia and diabetes mellitus were significant risk factors for all serious pulmonary infections. Unrelated donors are risk factor for post renal transplant pulmonary infections.

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