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Original Research Article

EPIDEMIOLOGY, CLINICAL PROFILE AND OUTCOME OF TUBERCULOSIS IN RENAL TRANSPLANT RECIPIENT

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Abstract Yogasathya

Background: Tuberculosis is one of the most common infections in renal allograft recipients, especially in developing countries and is responsible for significant morbidity and mortality. Our objective was to study the occurrence, risk factors and prognosis of tuberculosis infection in renal transplant recipients. **Materials and Methods:** A retrospective observational study of 335 renal transplant recipients in an Institute of Nephrology, Madras Medical College, Chennai. The demographic data, all relevant information about transplant, (donor source, delayed graft function, immunosuppressive regimen, co-morbidities, graft rejection) clinical manifestation, diagnosis and treatment of tuberculosis infection were analyzed. **Result:** Out of 335 renal transplant recipients, tuberculosis was diagnosed in 32 (9.5%) patients based on isolation of mycobacterium tubercle bacilli in 11(34.4%) patients, radiological evidence in 14 (43.8%) patients, histopathology in 3 (9.38%) and clinical evidence in 4 (12.5%) patients. The predominant presentation was pulmonary (37.1%), pleural (20%) and disseminated (11.4%). The major risk factors were delayed graft function (DGF), anti-rejection therapy, Hepatitis C viral infection (HCV), Cytomegalovirus (CMV) infection, and new onset diabetes after transplantation (NODAT). The mean time interval between transplantation and development of tuberculosis was 44.84 ± 37.66 months. All patients tolerated the anti-tuberculosis therapy (ATT) well. Mean duration of ATT was 11.31 ± 3.55 months. Most patients were treated with non-rifampicin based ATT (87.5%). Two patients (6.25%) died within one month after diagnosis of TB. **Conclusion:** The occurrence of tuberculosis in renal transplant recipients was 9.6%. The major risk factors are DGF, anti-rejection therapy, CMV, Hepatitis C infection and NODAT. The predominant presentation was pulmonary (37.1%).

INTRODUCTION

Chronic kidney disease is one of the leading cause of morbidity and mortality in India. [1-3] For patients with end stage renal disease, renal transplantation is the best form of renal replacement therapy and it is increasing exponentially. Infection is the most common cause of death in a renal transplant recipient in developing country contrary to west where cardiovascular mortality is the leading cause.[2] [4][5] Among the infections tuberculosis is one of the leading cause of morbidity and mortality in renal allograft recipient.

World Health Organization (WHO) global tuberculosis data base 2017, 30 high TB burden countries were identified, one of the country is India.[6] The incident of TB infection is also high due to other immunosuppressed conditions like HIV, Diabetes, Malignancy, CKD and malnutrition in India and other developing countries.[7] Because of emerging newer immunosuppression drugs and explosion of population and increased incidence of other immunomodulatory infections, renal allograft recipient may be at high risk for infection with mycobacterium tuberculosis.[8]

Studies shows that risk in solid organ transplant recipient is estimated to be 20 to 74 times higher than the general population. The incidence of the TB in India in 2022 was 196 per 100,000 population. Prevalence of active TB is estimated to be 1.2% to 6.4% in developed countries and up to 15% in highly endemic areas.[1][9]According to John et al in India, the incidence of TB in patients on maintenance dialysis is 8.7% and that in renal allograft recipient is 12.3%.[1] Early diagnosis and treatment may reduce the mortality of the renal allograft recipient. The diagnosis and treatment of tuberculosis is challenging in allograft recipient, because of varying degrees of manifestation and drug interaction.[9] The timetable

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of infections based on western data may not be applicable to Indian patients, because of high risk for multiple endemic pathogenic organisms, immunization status,virulence of the organism and the economic status of the patients.[9] Studies have shown that CMV infection increases the risk of TB and Hepatitis C infection increases the risk for TB, CMV and Nocardia.[8]

The objective of this study was to examine the occurrence, clinical profile and outcomes of tuberculosis in relation to different immunosuppressive regimens among renal allograft recipients.

MATERIALS AND METHODS

In this descriptive observational study, we have reviewed medical records of 335 renal transplant recipients in our department from November 2022 to August 2023, who are on regular follow up in our transplant OPD. Renal transplant recipients with stable graft function in the initial three months and on regular follow up were included in this study. Renal transplant patients on irregular follow up, patients who expired within three months of transplantation, patients without adequate documented case records were excluded in this study. All data were obtained from medical records and recorded in Excel sheet. Demographic data such as age, sex and the native kidney disease were recorded. Risk factors associated with Tuberculosis such as history of previous rejection diagnosed by renal biopsy, induction therapy used at the time of transplantation and immunosuppressive medication were documented. Other co-existing infection which was documented as a risk factors in other studies were also recorded. Natural history, outcomes were also evaluated, including complete cure, mortality and graft function. Tuberculosis was diagnosed based on bacteriological, radiological and histopathological evidence of Mycobacterium Tuberculosis bacilli and also diagnosed based on trial therapy response. The pulmonary disease was defined as the involvement of lung only and extrapulmonary tuberculosis was signified the involvement of a single extrapulmonary site. Disseminated tuberculosis refers to the concomitant involvement of at least two separate sites.

The risk factors studied were DGF[delayed graft function defined as the use of dialysis within seven days of the transplant), rejection episodes(rejection is defined by a decline in kidney function accompanied by well-established diagnostic features on kidney allograft biopsy), NODAT[diagnosis of NODAT based on the definition of diabetes mellitus described by the World Health Organization(WHO) and American Diabetes Association(ADA) guidelines], Immunomodulatory viruses like CMV and Hepatitis C virus and Induction Immunosuppressive drugs(is intense, prophylactic therapy used at the time of transplantation to prevent hyperacute rejection) like ATG (antithymocyte globulin) and Basiliximab(monoclonal antibody to Interleukin -2 receptor of T cells), maintenance triple immunosuppressive therapy with corticosteroid, one of the Calcineurin inhibitors (cyclosporine or tacrolimus)and antimetabolites(Azathioprine or Mycophenolate mofetil). The relationship between the above risk factors and occurrence of TB were also analysed. The radiological abnormalities in the X-ray, CT scan and PET scan were also analyzed if necessary. For the microbiological evidence the body materials like sputum, bronchoalveolar lavage(BAL), pleural fluid, urine ,lymph node, synovial tissue were subjected for AFB staining by Ziehl-Neilsen technique, Gene Xpert (NAAT-nucleic acid amplification test)-a molecular test for TB by detecting the presence of TB bacilli as well as testing for resistance to the drug Rifampicin. , cell cytology for supportive evidence of TB infection and the histopathological examination to look for giant cell, caseation and granuloma. Patients were treated with four drugs anti tuberculosis treatment(ATT) regimen including Rifampicin(R), Isoniazid(H), Pyrazinamide(Z) and Ethambutol(E). Patients who were on calcineurin inhibitor therapy were treated with Rifampicin free regimen because Rifampicin induces cytochrome -c 450 microsomal enzyme system which is responsible for metabolizing cyclosporine and prednisolone. This interaction reduces serum level of calcineurin inhibitors and prednisolone, leading to acute rejection. So Rifampicin should be avoided in renal transplant recipients. A quinolone with antimycobacterial property is usually added as a fourth drug in ATT instead of Rifampicin. The duration of regimen usually 9 months to 18 months based on severity of the disease and response of the treatment. The standard treatment at our institute was daily four drug regimen for three months, followed by two drug regimen for remaining period. The outcome was measured in term of morbidity (degree of graft dysfunction, adverse effects of ATT, recurrence of disease), complete cure and mortality.

A descriptive analysis of the data was performed by calculating frequencies and percentage of qualitative variables. Quantitative variables were analysed with chi-square test. A value of $p< 0.05$ was considered significance in all statistical analysis. The ethic committee of the MMC, Chennai approved this study.

RESULTS

Out of the 335 patients followed up, 229(68.4%) had received graft from living related donors. 35 episodes of tuberculosis infections were noted in 32(9.5%) patients.

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Table 1: Demographic data for Tuberculosis and Non-Tuberculosis group

Parameter	TB Group (n=32)	Non-TB group(n=303)	P value
Male: Female	28(87.5%): 4(12.5%)	235(77.5%): 68 (22.4%)	0.192
Age (years)	37.2±10.2	35.8±9.6	0.220
LRRT: DDRT[#]	20(62.5%): 12 (37.5%)	209 (69%): 94 (31%)	0.453
PreTx Diabetes[*]	3 (9.4%)	6 (2%)	0.013
PreTx HCV[*]	3 (9.4%)	2 (0.7%)	0.001
PreTx Tuberculosis[*]	0	4 (1.3%)	-

#-Live related renal transplantation: deceased donor renal transplantation, * - Pre-transplant status

Table 2. Risk factors analysis

Risk factors	TB Group(n=32)	Non-TB Group(n=303)	RR (Times)	CI-95%	P value
Induction agent[*]	7(21.9%)	76(25.0%)		0.628	0.628
Cyclosporine	19(59.4%)	86(28.4%)	3.2	1.6-6.2	0.001
Tacrolimus	11(34.4%)	188(62.3%)	0.36	0.18-0.72	0.005
DGF[†]	14((43.7%)	77(25.4%)	2.08	1.08-4.01	0.027
Rejection	8(25%)	86(28.4%)	0.99	0.55-1.7	0.975
NODAT	11(34.4%)	51(16.8%)	2.3	1.1-4.5	0.015
CMV	12(37.5%)	19(6.3%)	5.9	3.2-10.9	0.001
HCV	8(25%)	28(9.2%)	2.7	1.3-5.7	0.006
HBV	1(3.1%)	6(2.0%)	1.5	0.24-9.6	0.667

*: Antithymocyte Globulin or Basiliximab; †: Delayed Graft Function RR-relative risk

Fever (75%) and cough (44%) were the common presenting symptoms. Other symptoms were loss of appetite (18.7%), loss of weight (25%), dyspnea (9.4%), hemoptysis (3.1%), chest pain (3.1%), diarrhea (3.1%), abdominal pain (3.1%), and knee swelling (3.1%).

AFB were demonstrated in 11 (34.4%) patients. Among these, sputum AFB staining was positive in 5(15.6%) patients, Bronchoalveolar lavage(BAL) positive for AFB in 2(6.25%) patients, BAL Gene Xpert was positive in 2(6.25%) patients and Pleural Fluid Gene Xpert was positive in 2(6.25%) patients. The diagnosis was made with radiological examination for 14(43.8%) patients. Tissue histopathological diagnosis was done in 3(9.38%) patients. 4(12.5%) patients were treated with therapeutic trial of ATT for PUO.

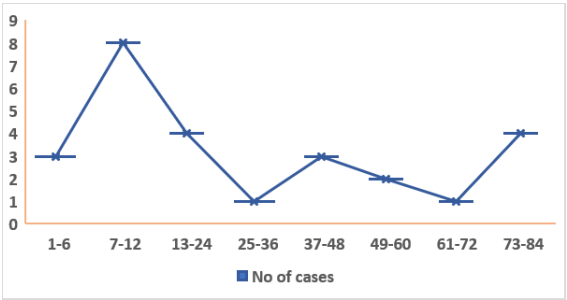

Fig.1 Distribution of post-transplant tuberculosis in post-transplant period in months.

The time interval from the onset of the symptoms to diagnosis was between 9 and 90 days with mean of 27.1±17.5 days. The mean time interval between transplantation and development of tuberculosis was 44.84 ± 37.66 months (range 5 to 120 months) Fig.2. According to the Rubin's time table, susceptibility period is divided into three groups: <1 month, 2-6 months, >6 months. But for the analytical purpose, it was divided as 1 to 6 months 3(9.4%) patients,7 to 12 months 8(25%) patiens,13 to 24 months 4(12.5%) patients,25 to 36 months 1(3.1%) patients ,37 to 48 months 3(9.4%),49 to 60 months 3(6.2%),61 to 72 months 1(3.1%), 73 to 84 months 4(12.5%), more than 84 months 6(18.8%) patients. So, the maximum incidence of post-transplant tuberculosis occurred at <12 months. The second peak incidence was at >72 months of post-transplant(Fig.1).

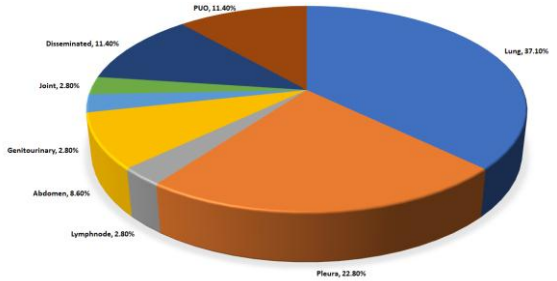

Fig.2 Various organ involvement of post-transplant tuberculosis.

Pulmonary and pleural tuberculosis were the most common manifestations of the disease. The organ system affected in the patients include the following: Lung (37.1%), Pleura (22.8%), Disseminated (11.4%), Abdomen (8.6%), Lymph node (2.8%), Joint (knee) (2.8%) and PUO (11.4%)(Fig.2). Among the 83 patients who had received induction therapy (ATG or Basiliximab), 7 patients developed TB in the post-transplant period. It was statistically not significant.

On examination of the association of the risk factors for occurrence of post-transplant tuberculosis compared with non-tuberculous allograft recipients (table 1) shows cyclosporine, DGF, NODAT, CMV, and HCV were statistically significant. The above variables positively correlated with the occurrence of post-transplant tuberculosis. The variables which did not show positive correlation with the occurrence of post-transplant tuberculosis were rejection (p=0.975)

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and Hepatitis B infection (p=0.667). The mean time of onset of TB in cyclosporine therapy was 48.8±38.8 months but in tacrolimus therapy it was 38.4±32.5 months. The mean age of onset of TB in cyclosporine based therapy was 35.8±10.01years but in tacrolimus based regimen it was 39.6±1o.9 years. Tacrolimus based immunosuppression negatively correlated with the occurrence of TB, which was statistically significant (RR 0.36; 95% CI 0.18 – 0.72, p=0.003). Other factors associated with post-transplant TB were fungal infections (15.6%) , herpes (15.6%).

Four patients who were not on calcineurin inhibitors were treated with Rifampicin based regimen. All patients received 4 drug combination ATT. Among these, 4 (12.5%) patients received Rifampicin based therapy (HREZ). 28 (87.5%) received Fluoroquinolone based therapy: Ofloxacin 25 (78.1%), Moxifloxacin 2 (6.2%), Levofloxacin 1 (3.1%). The average total duration of therapy was 11.31±3.55 months (6 to 18 months.). Twenty three (84.4%) patients successfully completed ATT regimen and 7 (21.8%) patients are still on ATT. Two (6.25%) patients developed adverse drug effect due to ATT viz. hepatotoxicity and peripheral neuropathy each occurring in 3.1% of patients. Two (6.25%) patients had recurrence of TB, one of them had a second recurrence. Two (6.25%) patients died within a month of initiation of ATT. One patient became hemodialysis dependent owing to graft failure.

The average serum creatinine before the onset of TB was 1.58±0.82 mg/dl (range 0.9 to 4.3 mg/dl). The mean serum creatinine after the TB onset was 1.75±0.88 mg/dl (range 0.7 to 5 mg/dl). Renal allograft dysfunction prior to TB was present in 17 patients. Graft dysfunction after the onset of TB was seen in 23 patients. We observed that occurrence of graft dysfunction after the onset of TB was statistically insignificant (p=0.109).

DISCUSSION

The prevalence of post-transplant tuberculosis in this study was 9.5%, similar to the prevalence observed in developing countries and in previous studies conducted in India(5 to 15%).[10] These rate are almost 49 times as high as the prevalence of TB in the general population(195/100,000 population) of India.[11] Tuberculosis occurring during the first year after transplantation may be due to intense immunosuppression reactivating latent tuberculosis, which is similar to results reported by john et al ,Jha et al and other studies in India.[2][12][13] The second peak occurring 6 years post-transplantation, may be due to new exposure to the endemic population. Tuberculosis should be considered as one of the differential diagnosis in patients with pyrexia of unknown origin during the first year of post transplantation.[5] The time interval between onset of symptoms and diagnosis of TB had a mean of 27.15±17.55 days(range 9 to 90 days). This may be due to similar manifestations of other infections in post-transplant immunosuppressed status. Clinical presentation of tuberculosis in immunocompromised individuals, including transplant recipients is often atypical and diverse. This lead to delay in diagnosis similarly reported in other studies , 10 to 102 days (median 25 days) in a Colombian study by Lina maria serna et al, 7 to 60 days in a Turkey study by Alev Atasever et al ,15 to 60 days by Anand m et al.[5][14]

Mean age of our patients was 32.28±10.27 years. There was no statistical difference in age(p=0.474) or gender(p=0.192) between the renal allograft recipients with or without TB.[15]

Pulmonary tuberculosis was observed in 37.1% of our patients with TB infection. It continues to be the most common form of tuberculosis in renal allograft recipients, similar to other studies like John et al (48.2%).[8][12] Fever was the most common symptom, followed by cough. Pleural effusion(22.8%) was the commonest extra pulmonary manifestation followed by disseminated TB(11.4%) ,it is similar to values reported by john et al(disseminated TB 19%).[4][12] The bacteriological and histological confirmation was obtained in 40.6 % of patients.

The major risk factors for post-transplant TB were delayed graft function (2.08 times), cyclosporine therapy (3.2 times), NODAT (2.3 times), other coexisting infections esp. CMV (5.9times) and Hepatitis C (2.7 times), which is similar to results reported in john et al.[8] In contrary to john et al, HCV infection was positively correlated as a risk factor for post renal transplant tuberculosis(p=0.006).[8][12] The relative risk of Hepatitis C infection was 2.7 times. Pre-transplant Diabetes also positively correlated as a risk factor for post-transplant tuberculosis compared with Non-TB population(p=0.013). Even though the incidence of TB occurrence after renal transplantation in Tacrolimus based regimen (mean 38.5±32.5 months) was earlier compared with Cyclosporine therapy (mean 48.8±38.9 months). Tacrolimus therapy less likely associated with development of TB (0.36 times). The mean age of development of TB in tacrolimus based regimen was 39.6±10.9 years but in cyclosporine based regimen was 35.8±10.01 years. It was statistically not significant(p=0.173) but in a Turkey study opposite result was reported(tacrolimus 24.2±7.4 years Vs cyclosporine 38.9±10.6 years).[15] Allograft rejection, hepatitis B and induction therapy were not associated with development of post-transplant TB(p>0.05).

The post renal transplant TB patients who were not on calcineurin inhibitors for maintenance immunosuppression therapy were started on Rifampicin based ATT. Rifampicin based or Non-rifampicin based four drugs ATT regimen were tolerated very well in 94% of patients. Among them 87.4% were treated with Fluoroquinolone instead of Rifampicin therapy.[2] Ofloxacin (78.1%) was the commonest fluoroquinolone used in non-rifampicin based ATT. Only 2 patients developed adverse drug effects [Hepatotoxicity (3.1%) and Peripheral neuropathy (3.1%)] due to the ATT but in many

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studies adverse effect of ATT high, Hepatotoxicity(41.7%)in a Colombian study.[5] Total mortality documented in our study was 6.25%(2 patients). One patient died as a result of hepatic failure after 10 days of therapy.

The average duration of ATT in our study was 11.31 ±3.55months (range 9 to 18 months), most of the study recommend early initiation and extended ATT regimen to prevent recurrence , in a Tunisian study by Karima Boubaker et al recommend at least 9 months.[2][7] The Graft dysfunction after the development of TB was statistically insignificant(p=0.109).

CONCLUSION

In conclusion, Tuberculosis remains a challenging opportunistic infection in the kidney transplant recipients with higher incidence and prevalence than general population.In the post transplant period , a high index of suspicion in this at-risk population would enable early diagnosis and appropriate treatment for TB. The interactions of the ATT drugs with the immunosuppressive agents have to be considered while prescribing and surveillance for adverse effects has to be done. The duration of treatment has to be prolonged and secondary prophylaxis has to be considered.

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Competing Interest

There is no competing interest

Authors Contribution

All authors in our study contributed to the data collection of the patients

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