PROFILE OF PULMONARY INFECTIONS IN RENAL TRANSPLANT PATIENTS

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ABSTRACT

BACKGROUND

Renal transplantation is a successful therapy for patients with end-stage kidney disease. In a country like India, where tuberculosis is highly prevalent, it poses immense diagnostic challenge. Proper knowledge about the microbiological spectrum would help to start appropriate therapy empirically, awaiting confirmation.

The aim of the study is to study the microbiological profile of lower respiratory tract infections in renal transplant recipients.

MATERIALS AND METHODS

Consecutive patients who presented to the transplant clinic with cardinal respiratory symptoms and fever were screened radiologically and an attempt to make a microbiological diagnosis was done with sputum or bronchial wash wherever needed. Setting- Prospective observational study conducted in the Department of Nephrology, Transplant Clinic, Rajiv Gandhi Government General Hospital and Madras Medical College. Post-renal transplant patients were followed up for 2 years between October 2014 - October 2016 and the development of pulmonary infection and the number of episodes were systematically recorded.

RESULTS

A total of 32 episodes of pulmonary infections were observed in 29 patients (23 males and 6 females). Bronchial wash had higher diagnostic yield than sputum. Triple drug immunosuppression comprising cyclosporine, prednisolone and azathioprine (75.8%) and episodes of acute graft rejection requiring pulse methylprednisolone (37.93%) were important prerequisites for developing pulmonary infection. Pseudomonas 12 (3%), Klebsiella 8 (25%) and Mycobacterium tuberculosis 8 (25%) were the most common organisms recovered.

CONCLUSION

Aggressive diagnostic modalities should be carried out for establishing the diagnosis. Empirical regimens should cover for Pseudomonas and Klebsiella. Tuberculosis should be sought for keenly. Mixed infections were also common in the study.

KEYWORDS

Microbiological Profile, Post-Renal Transplant, Immunosuppression, Bronchoalveolar Lavage.

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BACKGROUND

Pulmonary infections are one of the most frequent cause of morbidity and mortality among the post-renal transplant recipients. Differentiating pulmonary infectious and noninfectious complications like atelectasis, pulmonary oedema, pulmonary thromboembolic events and post-transplant malignancy is of paramount importance since the management differs.[1] Risk factors associated with the development of pulmonary complications are poorly understood. They can occur as a result of the mechanical ventilation performed during the surgery, the presence of arteriovenous fistulas, ureteric stents and because of delayed graft function.[2,3,4,5,6] Other factors responsible for acquiring infections are post-transplant immunosuppression, which is a major factor, pre and post-transplant diabetes mellitus, lack of hygienic practices, hot and humid climate, poor socioeconomic status and the endemic nature of certain infections in tropical countries.[7] Appropriate treatment requires knowledge about the microbiological profile of pulmonary infections and the time of development of such respiratory tract infections. Aggressive diagnostic approaches maybe required to make an early diagnosis and to start appropriate treatment. The present study was undertaken to know about the aetiological factors for respiratory infections in post-renal transplant patients, their common clinical presentation and the role of bronchoalveolar lavage in its diagnosis.

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MATERIALS AND METHODS

This prospective observational study was conducted in Department of Nephrology and Thoracic Medicine in Madras Medical College. The study was approved by the Institutional Ethics Committee of Madras Medical College; Government General Hospital, Chennai. Subjects were renal transplant recipients followed up in the Department of Nephrology, Rajiv Gandhi Government General Hospital. The study was conducted between October 2014 to October 2016. Transplant recipients attending the renal transplant clinic were included if they developed clinical and radiological (x-ray chest or chest CT) features suggestive of pulmonary infection. Patients who had already received antibiotics for more than 48 hours and who had absolute contraindication to undergo bronchoscopy were excluded.

Study Procedure- All the study participants were admitted and subjected to a comprehensive clinical assessment, which included a detailed history and thorough physical examination. The patients were evaluated in detail for the history of present illness, symptoms like fever, cough, haemoptysis, dyspnoea, chest pain, history of previous chest infection (pre and post-transplant), details of immunosuppression, past history of acute rejection and its therapy, recent intravenous antibiotics. History of other risk factors like diabetes (pre and post-transplant) and serological virology status, hepatitis B and C and CMV.

Sputum specimen was received from the patient on first day of admission submitted for direct smear examination by Gram's stain and staining for demonstration of fungal elements using KOH mount. Two specimen of sputum, one on first day of admission and two on second day of admission including an early morning sample was collected and submitted for Ziehl-Neelsen stain (Z-N) for Acid-Fast Bacilli (AFB). Patients not able to give good quality sputum were subjected to bronchoscopic lavage. The BAL specimen was submitted for Gram's stain and aerobic bacterial cultures, both qualitative and quantitative, Z-N stain for AFB and GeneXpert (CBNAAT), direct examination for fungal elements using relevant stains and fungal culture and GMS stain to identify Pneumocystis carinii. Data was analysed using SPSS Version 20. Categorical variables were expressed as percentage and mean with standard deviation were used for expression of continuous variables. Independent influence of potential risk factors was analysed for its association with pulmonary infections.

RESULTS

32 episodes of pulmonary infection occurred in 29 patients who were followed up post-renal transplant. Among the 29 patients, 27 reported once, one reported twice and another thrice. There were 23 males and 6 females (Table 1). The mean age of the patient studied was 31.8 years, which ranged from 18-53 years. Majority of the patients who came with pulmonary infection received their organ from a live-related donor, 25 (86.2%) patients out of 29, while the remaining 4 (13.8%) were from cadavers (Table 2). None of the patients had received influenza or pneumococcal vaccine in the past. None of the patients required mechanical ventilation.

	N=32	Percentage
Male	27	84
Female	5	16

Table 1. Showing the Gender Distribution in the Study

	N=32	Percentage
Live	27	84
Cadaver	5	16

Table 2. Donor Distribution of Renal Transplant Recipients

Predisposing Factors- The most important risk factor for developing pulmonary infection was history of acute graft rejection requiring pulse methylprednisolone 37.93% (11 cases), followed by post-transplant diabetes mellitus 13.8% (3 cases) past history of Cytomegalovirus infection. In a major proportion of cases 24.13% (7), no clear identifiable risk factors. The aetiology of CKD, which lead to transplantation did not play significant role as a contributing factor in developing pulmonary infection. The number of immunosuppressant received did play a role in causation, since cyclosporine, prednisolone and azathioprine based triple regimen have caused havoc. In all, 75.86% (22) of them who received the same had developed infection. MMF, tacrolimus and steroid-based triple regimen has been comparatively safe since only 4 (13.79%) had developed infection in spite of receiving three drugs.

Symptoms

Sl. No.	Symptoms	Number of Patients
1.	Fever	27
2.	Cough	22
3.	Loss of appetite	11
4.	Breathlessness	11
5.	Weight loss	6
6.	Chest pain	5
7.	Haemoptysis	2

Table 3. Showing the Most Common Symptoms in the Descending Order

The most common presenting symptom was fever followed by cough, loss of appetite, breathlessness, chest pain and haemoptysis (Table 3).

Time Table of Infection Post Transplantation- Most of the infectious episodes (12) has occurred after 2 years post transplantation and the first 6 months after transplantation (9). Most of the bacterial (7) and fungal (1 candida and 1 pneumocystis) infection has occurred between, 1-6 months post transplantation. 2 episode of mycobacterial infection has also occurred in this period. Mixed bacterial infection has also been observed in this period.

The second peak of bacterial infection has been observed after 2 years. Six episodes of bacterial infection and 5 episodes of Mycobacterial infection has occurred in this period. Out of the total 9 episodes, 5 episodes has

occurred in this period. Exotic bacteria like nocardia has also been observed in this period.

Period	n=32	Percentage
Less than 4 weeks	2	6
4 weeks to 6 months	7	21
6 months to 1 year	6	18
More than 1 year	16	50

Table 4. Showing the Time Table of Infection Post Renal Transplant

Overall, the most frequently observed bacteria is Pseudomonas, which has been observed in almost all the time interval followed by Mycobacterium tuberculosis (Table 4).

Spectrum of Respiratory Infection in Relation to Immunosuppressive Therapy-
Respiratory infections either bacterial, mycobacterial or fungal were common in patients with triple drugs immunosuppressive therapy with cyclosporin-A, prednisolone and azathioprine. Out of the 9 mycobacterial infections, 8 were present in patients on cyclosporine A containing immunosuppressive therapy.

Radiological Manifestation at Presentation- On analysing radiological manifestations of pulmonary infection, 23 (71.87%) patients had air space opacities/consolidation, 4 (12.4%) patients had pleural effusion, 1 patient (3.1%) had miliary nodules and another 1 (3.1%) fibrocavitary and was normal in 2 (6.2%) patients. Out of the total 16 episodes of bacterial infection, 12 (75%) presented radiologically as airspace opacities, 3 with pleural effusion and 1 with nodular opacity (nocardia) (Table 5).

	Air Space Opacities/Consolidation	Pleural Effusion	Nodules	Fibrocavitary	Miliary	Normal	Total
Bacterial infection	12	3	1				**16**
Tuberculosis	6			1	1	1	**9**
Aspergillus	1						**1**
Candida	2						**2**
PCP	1						**1**
Nondiagnostic	1	1				1	**3**
Total	**23**	**4**	**1**	**1**	**1**	**2**	**32**

Table 5. Various Radiological Manifestations of Pulmonary Infections

Tuberculosis presented with airspace opacity, cavity and miliary pattern. Fungal infections presented with airspace opacities. Three episodes of parapneumonic effusions were observed, and in one patient, the effusion was nondiagnostic.

Diagnostic Methods- 25 patients were able to bring out sputum. In 17 episodes, Gram stain was able to come up with a result. In majority of the case, it was gram-negative bacilli as was reflected in sputum culture and sensitivity where Pseudomonas and Klebsiella were the predominant species grown. KOH mount was positive in 1 patient, which grew Candida in fungal culture and sensitivity. Direct smear for AFB by Ziehl-Neelsen technique was positive in 2 cases. Sputum bacterial culture showed no growth in 12 patients (37.5%).

Apart from 2 patients for whom direct smear was positive for acid-fast bacilli, all other episodes (30) were subjected to bronchoalveolar lavage. Gram-negative bacilli were predominantly seen (19) in BAL Gram stain, which predominantly grew pseudomonas (8) and Klebsiella (2) in BAL bacterial culture and sensitivity. Both pseudomonas and Klebsiella grew in (2) instances. Mycobacterium tuberculosis was seen in BAL Ziehl-Neelsen staining in 7 cases and all the cases in turn were confirmed with GeneXpert BACTEC MGIT C/S, all were rifampicin sensitive. Mycobacterium tuberculosis was the sole organism grown in 6 cases, while in the remaining 1 case, it was coinfected with Flavobacterium and Pseudomonas. Nocardia, methicillin-sensitive Staph aureus, acinetobacter and Klebsiella coinfection were seen respectively in one case each.

Organism		N=32	Percentage
Bacteria (26)	Pseudomonas	12	37
	Klebsiella	8	25
	Staph. aureus	1	3
	E. coli	1	3
	Acinetobacter	1	3
	Nocardia	1	3
	Flavobacterium sps	1	3
	CONS	1	3
Mycobacteria		8	25
Fungus	P. carinii	1	3
	Candida	2	6
	Aspergillus	1	3

Table 6. Microbiological Profile of the Transplant Recipients

As far as yield of BAL in diagnosing fungal infection, candida was grown in 2 instances, Aspergillus coinfected with E. coli in 1 instance, Pneumocystis jirovecii in 1 instance. BAL showed no growth in 12 episodes (Table 6).

DISCUSSION

Pulmonary complications after kidney transplantation usually occurs in 5-24% of the patients, but according to some authors, the incidence can reach up to 37%.[8,9] The rate of first infections in the initial 3 years after kidney transplantation is 45.0 per 100 patient-years of followup as estimated using Medicare claims data collected by the U.S.

Renal Data System.[10] Bacteria has been found to be the major cause of post-transplant pulmonary infection. In the Indian studies, the incidence of bacteria has been found to range from 25% to 69.5%, while in the west, it is anywhere between 25-33%.[11] This wide variation in the incidence of bacterial pneumonia can be attributed to wide variation in the diagnostic methods used. From transtracheal aspiration to bronchoalveolar lavage, different methods has been employed in different studies, while sputum and BAL were the primary methods employed in this study.

In India, tuberculosis being an endemic disease poses a formidable challenge to the clinician dealing with transplant recipients, despite the advances in diagnostic facilities and chemotherapy.[12] This is expected since the prevalence of tuberculosis in general population in India is higher. Pulmonary tuberculosis has been reported to occur with 10-25 times higher frequency in immunosuppressed patients.[6] Recent Indian data shows a higher incidence of pulmonary tuberculosis in this group of patients ranging from 30-50%. Tuberculosis incidence of 50%. Jha V et al[13] reported an incidence of 30.7%. Vikram Kalra et al[14] found the incidence of tuberculosis in post-renal transplant patients to be 36.3%. As quoted in the previous study, this is probably because of the use of bronchoscopy in the isolation of the organism in the recent studies. Our study reported an incidence of 28.12% of pulmonary tuberculosis in the renal transplant recipients.

The time range for development of tuberculosis infection was from 2.7 months to 8.7 years with a mean of 3.38 years. 7 out of the 9 tuberculosis patients developed the illness in less than 6 years period from transplant surgery. All these 7 patients were on triple immunosuppressive drugs (cyclosporine, azathioprine and steroids). Of the 2 developing tuberculosis beyond 6 years duration, one was on non-cyclosporine containing immunosuppressive therapy (azathioprine and steroids) and the other on triple immunosuppressive drugs. This in accordance with the study by John et al, CMC, Vellore, determining a timetable for post-transplant infections in the tropics concluded that most patients on CsA who are likely to develop post-transplant tuberculosis will have developed the disease by six years.

P. Jiroveci is an opportunistic pathogen especially observed in patients with impaired cellular immunity. In our study, there was one episode (2.85%) of PCP. It presented in 5th month post-transplant. In recent studies in India, the incidence of PCP among this group of patients was from 6% to 27%.

Multiple organism infections were noted in 5 episodes (14.28%). 4 of them had 2 organisms and 1 case had 3 organisms as aetiology. Tuberculosis with Pseudomonas and Flavobacterium infection and Aspergillosis with E. coli was noted on each occasion and the other 3 were mixed bacterial infections, 2 cases with Pseudomonas and Klebsiella and 1 case with Acinetobacter and Klebsiella. More than one organism being the cause of infection has been seen in other studies too. In the study by Vikram Kalra et al, 31 out of the 44 episodes of pulmonary infection evaluated. Multiple aetiologies were found in 15 (34.1%) episodes based on BAL. Thus, it appears that the use of BAL maybe an important factor in isolation of more than one organism and establishing a multiple aetiology.

Herpes, influenza, parainfluenza and adenovirus are the group of viruses, which causes respiratory tract infections in renal transplant recipients. Among these, CMV is the most frequent pathogen encountered.[15,16] It frequently occurs 1-4 months after transplantation, when both allograft rejection and intensive immunosuppressive treatment occur. The clinical onset of CMV pneumonia is usually insidious with slowly progressing, relapsing fever, alternating between afebrile and 40°C along with fatigue. CMV infection was not well recognised among renal transplant recipients in tropical countries because of lack of proper diagnostic facilities.[17,18]

Would development of pulmonary infection be influenced by receiving the kidney from cadaver or live related donor is a matter of debate? Our study is slightly biased towards live-related donor kidney, because the number of kidney transplantation procedures performed with live-related donors outnumber the cadaver kidneys. A study of 1676 kidney transplant patients showed that the risk of developing infectious complications when receiving an organ from a living-related donor stands at 1.93 times (Odds Ratio (OR) = 1.93).[19] The primary kidney condition, which has led to an ESRD has not been responsible for the development of pulmonary complications.

Limitations- Our study did not include investigations related to viral aetiology due to lack of facilities to identify and isolate the same in our institution.

CONCLUSION

Pulmonary infection is still a major cause of morbidity and mortality in post-renal transplant recipients. The treating physician should try every means to make a diagnosis, since timely intervention would reduce the complication rate. Bacterial pneumonia especially Pseudomonas and Klebsiella were the predominant bacteria, empirical regimen should cover for these bacteria. Looking for tuberculosis in a country like India is always important and with the advent of rapid molecular diagnostic methods, earlier diagnosis and treatment is possible. Mixed infection is common among renal transplant recipients and search for the aetiologic agent should not stop at the isolation of one organism, especially if the response to therapy against a single aetiologic agent is partial and/or delayed. The presence of more than one organism should be conclusively ruled out.

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