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Evaluation of Clinico-Pathological Spectrum in Renal Allograft Biopsies at JIPMER

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Abstract

Background: Renal transplant patients in JIPMER undergo a systematic post-transplant follow-up in order to identify any new co-morbidity as well as detect abnormalities in graft function at the earliest and institute appropriate management. The renal allograft biopsy is one of the principal tools used by the nephrologists to diagnose any such episodes of graft dysfunction.

Objective: The aim of this study were to identify the chief causes of end stage renal disease and co-morbid conditions, to study the number of biopsies taken for each patient as a function of time and to assess the usefulness of an allograft biopsy.

Materials & Methods: A total of 120 renal transplants were carried out in JIPMER in a period of 5 years from March 2012 to March 2017. 78 patients who underwent renal allograft biopsies were included in the study, serial measurement of serum creatinine and change in dose of immunosuppressant were recorded and correlated with the biopsy findings.

Results: In exactly two-thirds of the patients (52) the cause for ESRD (End-Stage Renal Disease) could not be determined; in the remaining 26 secondary FSGS was the leading cause for ESRD. Systemic Hypertension (59%) was found to be the major co-morbidity in renal transplant patient, 82% patients underwent renal biopsy within the first 3 months after transplant and elevation in serum creatinine was the indication for most of the biopsies. A large fraction of the patients (64%) improved upon instituting appropriate treatment measures based on biopsy findings in correlation with other clinical and laboratory data.

Conclusion: Our findings suggest that for our setting renal allograft biopsy is the major modality of diagnosing the cause for derangement in graft function, especially in the early post-transplant period. Management course decided on the basis of biopsy findings results in improved patient outcome in a majority of cases.

Keywords: End-Stage Renal Disease; Allograft biopsy; Renal transplant

Introduction

Renal transplant patients undergo a vigilant follow-up in the post-transplant period. This enables a close monitoring of the renal allograft function. Immunosuppressant dose titration is critical in order to balance potential nephrotoxicity with the benefit of immunosuppression as well as prompt detection and treatment of various co-morbidities, often seen in these patients. Renal allograft biopsy is an important tool to study the status of the renal allograft [1]. It is the accepted gold standard for investigating episodes of graft dysfunction in the post-transplant period [2-5]. The major categories of graft dysfunction are acute or chronic rejection, CNI toxicity, infections or recurrence of primary renal disease [4,6]. Renal biopsy findings result in altering management decisions in approximately 40% of instances with presumptive diagnosis made on the basis of clinical and laboratory findings [4,5,7-9]. The follow-up of patients undergoing renal transplant over duration of 5 years was studied by a retrospective cohort method. The major co-morbidities affecting these patients were documented. The number of biopsies taken for a recipient after various time intervals was recorded along with the indication for each biopsy. In an effort to further analyze the usefulness of the renal allograft biopsy, the alteration in management course i.e. change in immunosuppressant dose done in accordance with the biopsy findings was correlated with improvement in graft function.

Objectives

The aims of this study were to:

1. Identify the spectrum of disease conditions causing morbidity in renal transplant recipients.
2. Determine the proportion of transplant recipients undergoing renal biopsy in first 3 months, 4-12 months and >12 months after transplantation.

3. Analyze the spectrum of clinical indications for initial graft biopsy and repeat graft biopsies.
4. Correlate the biopsy findings with clinical diagnosis.

Methodology

One hundred and twenty renal transplants were performed in JIPMER over duration of 5 years from March 2012 till March 2017. It is a retrospective observational study, all the patients who have undergone renal transplantation at JIPMER with pre-transplant work up and post-transplant follow-up at JIPMER were included in the study. Institute Scientific Advisory committee and Ethical committee approval was obtained for the study. The case records of these patients were studied from the Transplant Clinic in the Department of Nephrology, JIPMER. Biopsy records and other laboratory information of the transplant patients were retrieved from the Hospital information system. 78 of these patients were found to have undergone allograft biopsies for these patients the basic disease leading on to End-Stage Renal Disease (ESRD) was analyzed along with the co-morbidities developed in the post-transplant period. For a majority of the patients, the basic disease leading on to renal failure remained undetermined. Percentage analysis was done for End-Stage Renal Disease (ESRD) patients with an established renal pathology. The major co-morbidities were found to be systemic Hypertension (HTN), NODAT (New Onset Diabetes after Transplantation), anemia, urinary tract infections (UTI) and acute gastroenteritis. Again, percentage analysis was done to analyze the prevalence of each of these conditions. A total of 127 renal biopsies were studied in the post-transplant period. The details of date and indication for biopsy were collected from the case records. The proportion of patients undergoing biopsy after various time intervals after the transplant, i.e. first 3 months, 4-12 months and >12 months was calculated, the indications for the biopsies were also studied. The histopathology findings were classified as normal, immune-mediated rejection, CNI toxicity and infection. For each biopsy, the alteration in immunosuppressant dose, if any was correlated with an improvement in graft function measured as a fall in serum creatinine level in an attempt to correlate the histopathological diagnosis with the clinical diagnosis arrived at by the nephrologist.

Results

Out of the 120 patients who underwent renal transplant, 27 did not undergo post-transplant biopsies, for 12 patients follow-up records were not available and 3 of them had either inadequate or post-mortem biopsies. All the biopsies were performed under ultrasound guidance and 16 gauge needles was the one that was commonly used. Blood pressure was brought under control as much as possible before the biopsy. In high risk patients, 18 gauge needles were used to perform the renal biopsy in our centre. No patient had any major complications secondary to renal biopsy in the post-transplant period except five patients who had transient hematuria. In two-thirds of these patients (52 of 78), the cause for ESRD remained undetermined. Of those with an established basic disease secondary FSGS was the leading cause of renal failure (6 patients), followed by IgA nephropathy (5 patients) and diabetic nephropathy (4 patients). The other causes included post-partum renal cortical necrosis, adult dominant polycystic kidney disease (ADPKD), congenital obstructive uropathy (Posterior urethral valve and pelvi-ureteric junction obstruction), hypertensive nephrosclerosis, renal stone disease, Ectopic single contracted kidney, Henoch Schonlein purpura nephritis and chronic interstitial nephritis (Table 1 and Figure 1).

S. No.	Cause	Number of patients
1	Undetermined	52
2	Secondary FSGS	6
3	IgA nephropathy	5
4	Diabetic nephropathy	4
5	Post-partum renal cortical necrosis	2
6	ADPKD	2
7	Congenital obstructive uropathy	2
8	Hypertensive nephrosclerosis	1
9	Renal stone disease	1
10	Ectopic single contracted kidney	1
11	HSP nephritis	1
12	Chronic interstitial nephritis	1
	Total	78

Table 1: Cause for ESRD in renal transplant recipients.

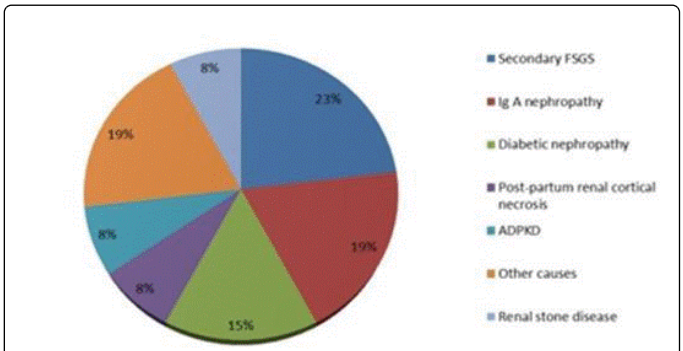

Figure 1: Causes for ESRD in renal transplant recipients.

Overall, 59% of the patients had systemic hypertension as an associated co-morbidity, 42.3% patients developed New Onset Diabetes after Transplantation (NODAT), 30.8% patients had associated anemia, 19.2% patients had episodes of UTI and 9% patients had episodes of acute gastroenteritis. Hypothyroidism was seen to be associated with 7.7% of patients (Table 2).

S. No.	Co-morbidity	% of patients
1	Systemic Hypertension	59
2	NODAT	42.3
3	Anemia	30.8
4	UTI	19.2
5	Acute gastroenteritis	9
6	Hypothyroidism	7.7

Table 2: Associated co-morbidities in renal transplant recipients.

During the first three months after transplant 82% patients had episodes of graft dysfunction necessitating a biopsy, repeat biopsies were required for 41% patients. In the time period between 4-12 months, 48.7% of the patients underwent biopsies and 19.2% patients underwent repeat biopsies. Only 28.2% of patients required a biopsy after 1 year while 9% of patients required repeat biopsies in this duration (Table 3).

S. No.	Time period	% of patients undergoing biopsy	% of patients undergoing repeat biopsy
1	First 3 months	82	41
2	4 to 12 months	48.7	19.2
3	More than 12 months	28.2	9

Table 3: Biopsies required in various time periods after transplant.

Analysis of the clinical indications for the biopsies revealed that 93.8% of the biopsies had been taken on the basis of an elevated serum creatinine level, 4.7% of the biopsies were indicated because of a delayed or slow graft function diagnosed due to inadequate urine output (Table 4).

S. No.	Indication	No. of biopsies	% of biopsies
1	Elevated serum creatinine	119	93.8
2	Delayed graft function	6	4.7
3	Persistently delayed graft function	1	0.8
4	Unexplained proteinuria	1	0.8

Table 4: Indications for biopsies in post-transplant period.

Upon analyzing the histopathological findings, it was found that 34.6% of the biopsies had normal light microscopy and no evidence of immunoglobulin deposits on immunofluorescence. In 27.6% biopsies, immune mediated rejection (both early and late cellular and antibody mediated rejection) was found 13.4% biopsies suggested CNI toxicity as the diagnosis while in 24.4% of the biopsies infection was found to be the cause of graft dysfunction (Figure 2).

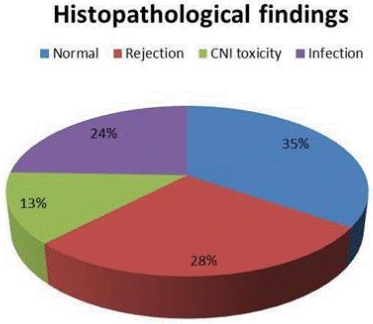

Figure 2: Histopathological findings in post-transplant.

On correlating the histopathological diagnosis with the change in immunosuppressant dose, it was found that for 59.1% of patients with a histopathologically normal biopsy, no change in immunosuppressant dose was made for 25.7% of patients with biopsy findings suspicious of rejection an increment in immunosuppressant dose was made.

In 82.4% of patients with biopsy suggestive of CNI toxicity, a reduction in immunosuppressant dose was made, in 64.2% of biopsies, a reduction in serum creatinine was seen with improvement in renal function, while in 15.4% serum creatinine remained persistently elevated. An increase in serum creatinine was seen in 20.3% of the patients after therapeutic intervention based on biopsy findings (Tables 5 and 6).

Biopsy finding	No change	%	IS dose increased	%	IS dose decreased	%	Total	%
Normal	26	59.1	7	15.9	11	25	44	100
Rejection	17	48.6	9	25.7	9	25.7	35	100
CNI toxicity	1	5.9	2	11.8	14	82.4	17	100
Infection	22	71	3	9.7	6	19.4	31	100
Total	66	52	21	16.5	40	31.5	127	

Table 5: Correlation of biopsy finding with change in immunosuppressant (IS) dose.

S. No.	Change in creatinine	No. of biopsies (Total 123)	% of biopsies
1	Decrease	79	64.2
2	Increase	25	20.3
3	No change	19	15.4

Table 6: Change in serum creatinine after biopsy on follow-up.

Only 4 of the 120 patients who underwent renal transplants had failure of the graft and 2 of the patients had repeat transplantation, there was recurrence of native disease in 2 of the recipients. 11 patients died after renal transplantation and sepsis was the cause in 55% of the patients.

Discussion

Renal biopsy is the gold standard in the assessment of deterioration of renal function of both native and allograft kidney. The disease

activity, severity and chronicity and the nature of the disease process viz., rejection, recurrence of the native disease, infections, drug toxicities or occurrence of *de-novo* new pathology can be identified by findings in the renal biopsy [10]. The most common indications for renal biopsy in the post-transplant setting were renal function deterioration or proteinuria. In our study, the indication for 94% of the biopsies was elevated serum creatinine and reduced estimated glomerular filtration rate (eGFR). We had only one patient who had a renal biopsy secondary to unexplained proteinuria. Other major indications in our centre were delayed and slow graft function or persistent delayed graft function (Table 7).

S.No	Reference study	Total biopsies studied	Common indications
1	Tsai et al. [10]	1563	Elevation of serum creatinine and unexplained proteinuria
2	Our study	127	Elevation of serum creatinine (94%). Uncommon indications - delayed and slow graft function, persistently delayed graft function and unexplained proteinuria

Table 7: Indication for renal biopsy.

S.No	Reference study	Total biopsies studied	Common Complications reported
1	Tsai et al. [10]	1563	Major complications - 2.8% Minor complications - 10%
			Arteriovnous fistula, Hemoglobin decline, gross hematuria, and hematoma
2	Canelas et al. [11] (2014)	390	Major complications requiring transfusion, embolisation, surgical intervention or death - 5.9%
			Minor complications - hematoma, hematuria and fever - 6.9%
3	Our study	127	No major complications Minor complication - Transient hematuria - 4%

Table 8: Complications from renal biopsy.

S.No	Reference study	Total transplant patients studied	Incidence of Biopsy proven acute rejection (both Early and late acute rejection)
1	Koo et al. [12]	709	30%(198)
2	Garcia et al. [13]	175	14.3%(25)
3	Our study	35	27.60%
4	OPTN/UNOS 2012 [14]	Guidelines	25%

Table 9: Incidence of acute rejection.

Renal biopsy is relatively a safe procedure and in our centre, we report only minor complications accounting of 4% of the patients. This is comparable to the results in other centers. None of our patients needed blood transfusion, admission or surgical intervention due to post-renal biopsy complications (Table 8) [11].

In our study, the incidence of biopsy proven acute rejection in both early (<3 months) and late (>3 months) after the transplant accounted for 27.6% of the patients. This was similar to the 23% rejection reported in the 2012 OPTN/UNOS records and Koo et al. (Table 9) [12-14]. In our study, 31 patients had biopsy proven evidence of infection including infections with BK virus, Cytomegalovirus and acute pyelonephritis (both early and late defined as within 6 months and after 6 months respectively). This accounted for 24.4% of post-transplant biopsies. 79% of the patients showed recovery from infection and improvement in renal function after initiation of appropriate treatment with biopsy findings. Majority of the patients required decrease in dose of immunosuppression with administration of antibiotics. In few patients, the dose of immunosuppression was not decreased due to concomitant rejection, 2 of the patients with biopsy proven acute graft pyelonephritis showed persistent graft dysfunction in spite of appropriate treatment. In our study, 5% of transplant patients (6 of the total 120) died due to sepsis. However, the total mortality in transplanted patients in our setting was 10% and 4 of the 120 patients (3%) had graft failure of which two of the patients underwent repeat transplantation. Our findings are better than the results described by Varma et al. who described mortality rate of 15% and almost most of the patients in their series, did not recover baseline renal function [15]. 28% of their patients had bacteremia at presentation, this is explained by the heterogeneous policies in definition of acute graft pyelonephritis and post-transplant management protocols. However, our results are comparable with Kayler et al. [16]. The major challenge in the interpretation of biopsy findings particularly in the context of viral infections is the concomitant interstitial and tubular infiltration by lymphocytes, mimicking cellular rejection. Thus correct interpretation of subtle morphological findings and good clinico-pathological correlation is extremely critical in appropriate management of these patients.

The strength of our study is availability of clinical, laboratory, drug details and biopsy records of all the patients with good follow-up of over 1 year in majority of the patients. However, our study is limited by the retrospective nature of the study, small sample size and difficulties in analyzing the different treatment strategies which vary according to the clinical manifestations and laboratory back-up available at the given time.

Summary

Our study highlights that most (2/3rd) of the patients requiring transplantation in our setting do not have the diagnosis for the cause of ESRD. In the subset of patients with known cause for ESRD, focal segmental glomerulosclerosis followed by IgA nephropathy and diabetic nephropathy were the common indications for renal transplant. Renal biopsy was the major diagnostic modality in the early post-transplant period (<3 months) and the number of repeat biopsies significantly decreased after 1 year of transplantation. The major indication for renal biopsy in our center was elevated serum creatinine with abnormal renal function, the other common indications were delayed graft function, slow graft function and proteinuria.

In our center, 25.75% of the transplant recipients had biopsy proven evidence of rejection while 33% of the patients had infections due to post-transplant immunosuppression. Most of the transplant biopsies (39.4%) of the patients had normal light microscopy while 13.4% patients had calcineurin inhibitor toxicity. Majority of the patients (65%) responded to appropriate treatment measures initiated based on biopsy findings in correlation with other clinical and laboratory data, while 15% had persistent renal dysfunction, 20% of the patients had deterioration in renal function.

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