The Relationship Between Histopathological and Laboratory Findings in Kidney Transplant Recipients

Böbrek Nakli Alıcılarında Histopatolojik ve Laboratuvar Bulguları Arasındaki İlişki

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ABSTRACT

Objective: In this retrospective study, we aimed to clarify the reasons for high creatinine levels and proteinuria in kidney transplants.

Material and Methods: The research data were obtained from patient files and the hospital database.

Results: Ninety-two patients, consisting of 24 females and 68 males, were biopsied. Histopathological examination of the biopsy samples showed borderline changes in 20 patients, acute antibody-mediated rejection (AMR) in two, chronic active AMR in 10, acute T-cell-mediated rejection (TCMR) in seven, recurrence of the primary disease or de novo glomerulonephritis in eight, coagulation necrosis in one, tubular atrophy and interstitial fibrosis in nine, calcineurin inhibitor drug toxicity in six, and polyomavirus nephropathy in seven. Average creatinine was 2.58±1.1 mg/dl. The proteinuria levels ranged from 83 to 12600 mg/day with the average value being 2142±2619 mg/day. Among the patients with a proteinuria value of less than 1000 mg/day, two had acute AMR, three chronic active AMR, 21 acute TCMR-borderline, and seven chronic active TCMR, and 12 biopsies revealed other causes. For the 1000-3500 mg/day proteinuria group, five chronic active AMR, two acute TCMR-borderline, and five chronic active TCMR were identified, and 11 biopsies indicated other causes. Lastly, of the patients with a proteinuria level of greater than 3500 mg/day, two had chronic active AMR, four acute TCMR-borderline, and eight chronic active TCMR, and seven biopsies revealed other conditions.

Conclusion: Diagnosis of renal allograft biopsies may vary from one center to another due to different diagnostic approaches to dysfunction and proteinuria in renal allografts.

Key Words: Proteinuria, Rejection, Renal Transplant Biopsy

ÖZ

Amaç: Bu retrospektif çalışmada, böbrek nakli olan hastaların yüksek kreatinin düzeyi ve proteinüri nedenlerini bulmayı amaçladık.

Gereç ve Yöntemler: Araştırma verileri hasta dosyalarından ve hastane veri tabanından alınmıştır.

Bulgular: 92 hastadan böbrek greft biyopsisi alındı. 24'ü kadın, 68'i erkekti. Biyopsilerin histopatolojik incelemesinde 20 sınırda değişiklik, 2 akut antikor aracılı rejeksiyon (AAAR), 10 kronik aktif AAR, 7 akut T hücre aracılı rejeksiyon (THAR), 8 birincil hastalık nüksü veya de novo glomerulonefrit, 1 koagülasyon nekrozu tespit edildi. 9 tübüler atrofi ve interstisyel fibrozis, 6 kalsinörin inhibitörü ilaç toksisitesi ve 7 polyomavirüs nefropatisi tanısı verildi. Ortalama kreatinin 2,58 ± 1,1 mg/dl idi. Proteinüri değerleri 83-12600 mg/gün ve ortalama proteinüri 2142 ± 2619 mg/gün idi. Proteinürinin 1000 mg/gün' den azında 2 akut AAR, 3 kronik aktif AAR, 21 akut THAR-borderline, 7 kronik aktif THAR ve diğer grubunda 12 biyopsi vardı. Proteinürinin 1000-3500 mg/gün arasında 5'i kronik aktif AAR, 2 akut THAR-borderline, 5 kronik aktif THAR ve diğer grupta 11 biyopsi vardı. 3500 mg/gün üzerindeki proteinüri, 2 kronik aktif AAR, 4 akut THAR-borderline, 8 kronik aktif THAR ve diğer grupta 7 biyopsi vardı. Rejeksiyon, rejeksiyon olmayan ve polyomavirüs nefropatisi olarak üç gruba

ayırdığımız zaman proteinüri açısından istatistiksel olarak anlamlı bir fark rejeksiyon olmayan grup ve polyomavirüs nefropatisi grubu arasında çıktı.

Sonuç: Renal allogreftte görülen disfonksiyon ve proteinüriye farklı tanı yaklaşımı nedeniyle renal allogreft biyopsilerinin tanıları merkezden merkeze farklılık gösterebilir.

Anahtar Sözcükler: Proteinüri, Rejeksiyon, Böbrek nakil biyopsisi

INTRODUCTION

In renal allograft dysfunction, reasons for failure include renal, pre-renal or post-renal causes, rejections (acute or chronic), calcineurin inhibitor (CNI) toxicity, polyomavirus (BK) toxicity, recurrent and *de novo* diseases, ischemic injury, hypertension, vesicoureteral reflux, pyelonephritis, and acute interstitial nephritis (1). The search for accurate noninvasive predictors of acute rejection is ongoing and recent literature describes novel plasma and urine-based biomarkers, as well as transcriptional profiling methods with high potential for clinical applicability (2). Since the current technology does not offer an alternative method for histopathological diagnosis, renal biopsy, despite being interventional, remains the most definitive diagnostic tool.

Based on the findings obtained from renal biopsies, clinicians decide on treatment options and predict the prognosis. The Banff classification, updated in 2013, has become the standard classification method for renal transplant pathologies (3).

In this retrospective study, we aimed to examine the indication biopsies of renal transplant recipients who underwent allograft biopsies in our center, and evaluate the relationship between histopathological diagnoses and laboratory findings.

MATERIAL and METHODS

Study Sample

Of the patients receiving a kidney transplant at our Transplantation Center or presenting at our organ transplantation center after receiving a kidney transplant at other domestic and international institutions, 92 that underwent renal allograft biopsies between January 2009 and June 2013 were included in the study. The research data were obtained from the patient files, cards and hospital database. The following information was recorded about the patients undergoing biopsy: gender, age, primary disease, donor source (cadaver, living), donor age, mismatch count, pre-transplant renal replacement therapy, presence of pre-transplant hepatitis, discharge after transplantation, creatinine, estimated glomerular filtration rate (eGFR) and proteinuria values at biopsy, renal biopsy results (all Banff scores and diagnosis), treatment received at biopsy, last checked creatinine, graft status, post-transplant diabetes mellitus, hypertension, hyperuricemia, and hyperlipidemia.

After pre-renal and post-renal causes were ruled out for the elevated serum levels, a renal biopsy was performed. Acute kidney injury was defined as a sudden rise (≥0.3 mg/dl) or an increase of more than 50% in serum creatinine (1.5 times) within 48 hours or a decrease in urine output (reduced urine output less than 0.5 ml/kg/hour for more than six hours) (4). Slow graft function was defined as slow renal function at one-week post-transplant and serum creatinine levels of 3 mg/dl or greater and lack of dialysis requirement (5). Delayed graft function was defined as post-transplant dialysis requirement for one-week or longer (6). Rapid deterioration of graft function was defined as an increase in creatinine levels by ≥50% and slow deterioration of graft function as an increase in creatinine levels by less than 50% during follow-up.

This study was approved by the Ethics Committee of our University Medical Faculty.

Biopsy Procedure

Hematoxylin-eosin and periodic acid–Schiff staining of the sections was performed in the laboratory. Immunohistochemical studies were conducted using a material-reserved immunofluorescent analysis with antibodies for IgA, IgM, IgG, C3, and fibrinogen at a separate session. In addition, C4d staining was carried out. Histopathological analysis was performed based on the Banff classification of 2009.

Statistical Evaluation

The results were analyzed using the Statistical Package for Social Sciences (SPSS) v. 18. Compliance with normal distribution was analyzed by the Shapiro-Wilk test. For the comparison of the quantitative data, the Kruskal-Wallis test was used, while post-hoc analysis was conducted using the Mann-Whitney U test and the Sidak correction method. Lastly, we used Spearman's rho test to measure the correlation between numerical variables. For statistical significance, the alpha level was set at 0.05.

RESULTS

The current study evaluated various features of 92 kidney transplant recipients who underwent renal allograft biopsies at our center between January 2009 and June 2013. Table I shows the demographic characteristics and clinical data of these patients. The donor and recipients

Table I: Demographic characteristics and clinical data.

Recipient Factors	**Average**	**Minimum- Maximum**
Transplant Age (years)	30.4 ± 10.1	14 – 56
Gender (M / F)	24/68	
Pre-transplant hepatitis (B/C/B+C)	9/4/1	
Pre-transplant RRT (HD/PD/HD+PD)	62/15/1	
Preemptive	12	
Donor Factors	**Mean ± Sd**	**Min-Max**
Donor Age (years)	42.3 ± 13.4	5-72
Transplant Factors		
First/second transplant		88/4
Living/Cadaveric		81/11
Mismatch Count (0/1/2/3/4/5/6)		4/2/8/36/14/13/5
Donor source (Relative/Not Relative)		39/52
Patients with Delayed Graft Function		10 (11%)
Induction Treatments (None/ATG/IL2 monoclonal antibody)		30/19/37
Number of Rejections before Biopsy (0/1/2/3)		46/31/7/4
Treatment Received at Biopsy (Steroid/Steroid+ATG/ATG/ steroid+plasmapheresis/ IVIG steroid+ATG+plasmapheresis)		(26/9/9/1/1/1)

M: Male, **F:** Female, **RRT:** Renal Replacement Treatment, **HD:** Hemodialysis, **PD:** Peritoneal Dialysis, **ATG:** Anti Thymocyte Globulin, **IVIG:** Intravenous Immune Globulin

Table II: Histopathological diagnoses based on biopsy results and biopsy counts.

Biopsy Diagnoses	**Count**
Acute antibody-mediated rejection	2
Chronic active antibody-mediated rejection	10
Borderline changes	20
Acute T-cell mediated rejection (type 1A)	5
Acute T-cell mediated rejection (type 1B)	1
Acute T-cell mediated rejection (type 2B)	1
Chronic active T-cell mediated rejection	22
5 I (mild IF-TA)	5
5 II (moderate IF-TA)	3
5 III (severe IF-TA)	1
Drug toxicity	5
BK nephropathy	7
MPGN	1
IgA	4
FSGS	4
Coagulation necrosis	1

were relatively young, with a mean age of 42.3 (5-72) and 30.4 (14-56) years, respectively. The rate of living donation was much higher than cadaveric donation (81 patients and 11 patients, respectively).

The causes of end-stage renal failure included vesicourethral reflux (n=11), focal segmental sclerosis (FSGS) (n=7), nephrolithiasis (n=6), membranoproliferative glomerulonephritis (MPGN) (n=4), familial Mediterranean fever (FMF) (n=3), polycystic kidney disease (PCKD) (n=2), crescentic glomerulonephritis (n=2), type I diabetes mellitus (DM) (n=1), type II DM (n=1), Alport syndrome (n=1), IgA nephropathy (n=1), hypertension (HT) (n=1), systemic lupus erythematosus (SLE) (n=1), posterior urethral valve (n=1), and unknown reasons (n=50).

The time of biopsies ranged from post-transplant day 4 to month 155. For each patient, the results of only one biopsy were evaluated. Table II shows the histopathological diagnoses based on biopsy results and biopsy counts.

Table III shows the laboratory findings at the time of renal biopsy. When renal biopsies performed, the creatinine level was 2.5 mg/dl (0.9-5.8) and the proteinuria level was 2142 mg/day (83-12600).

Renal biopsy indications included rapid deterioration of graft function (n=39), slow deterioration of graft function (n=27), investigation of proteinuria (n=25), and primary graft non-function (n=1).

Table IV presents the time of biopsies and the diagnoses made based on the biopsy results. In the first year, acute T-cell-mediated rejection and non-rejection related reasons were identified. In the following years, most patients were

diagnosed with chronic active T-cell-mediated rejection and non-rejection-related conditions.

The distribution of biopsies according to diagnoses and proteinuria levels is shown in Table V. In non-nephrotic-range proteinuria, different diagnoses were observed whereas in nephrotic-range proteinuria, the chronic component of rejection was higher.

In addition, the majority of our patients with proteinuria of 1000-3500 mg/day were gathered in a separate group comprising diagnoses of drug toxicity (n=3), IF/TA (n=3), FSGS (n=1), IgA nephropathy (n=2), MPGN (n=1), and BK nephropathy (n=1).

Of the 92 patients, 31 lost their grafts. The results of the biopsy conducted before graft loss showed chronic active T cell-mediated rejection in 11 patients, borderline changes in seven, drug toxicity in three, BK nephropathy in three, chronic active antibody-mediated rejection in two, FSGS in one, acute T-cell mediated rejection type 1 in one, IgA nephropathy in one, acute antibody-mediated rejection in one, and coagulation necrosis in one.

Biopsy diagnoses and proteinuria levels are shown in Table VI. The patients were classified as rejection, non-rejection and BK nephropathy groups, and the last group had significantly lower proteinuria levels than the former two groups ($p<0.05$).

Table III: The laboratory findings at the time of renal biopsy.

	Status at biopsy		
	Mean	**Min. Max.**	**Median**
Patient age at biopsy (years)	35.3 ± 37.6	0.27 - 57	24.9
Serum creatinine level at biopsy (mg/dl)	2.5 ± 1.1	0.9 - 5.87	2.34
Proteinuria level at biopsy (mg/day)	2142 ± 2619	83 - 12600	1000
GFR at biopsy (ml/min)	35.3 ± 18.9	10 - 92	31.5

Table IV: Biopsy ages and diagnoses and biopsy counts.

Biopsy age	**Number of biopsies receiving diagnosis***				
	1	**2**	**3**	**4**	**5**
0 - 12 months	2	0	11	1	19
12 - 36 months	0	4	12	7	5
36 months later	0	6	4	14	7

***: 1.** Acute antibody-mediated rejection, **2.** Chronic active antibody-mediated rejection, **3.** Acute T-cell mediated rejection, borderline, **4.** Chronic active T-cell mediated rejection, **5.** Other.

Table V: The distribution of biopsies based on the diagnoses and proteinuria levels.

Proteinuria level (mg/day)	**Number of biopsies receiving diagnosis***				
	1	**2**	**3**	**4**	**5**
0 - 1000	2	3	21	7	12
1000 - 3500	0	5	2	5	11
Over 3500	0	2	4	8	7

***: 1.** Acute antibody-mediated rejection, **2.** Chronic active antibody-mediated rejection, **3.** Acute T-cell mediated rejection, borderline, **4.** Chronic active T-cell mediated rejection, **5.** Other

Table VI: Biopsy diagnoses and proteinuria levels

Diagnoses	**Proteinuria (mg/day)**		
	Mean ± SP	**Min. Max.**	**Median**
Rejection Group	2,027 ± 2,473	83 - 10,218	690
Non-Rejection Group	2,952 ± 3,097	176 - 12,600	1,746
BK nephropathy	448 ± 546	112 - 1,666	263

Transplant glomerulopathy (cg1-3, double contours on glomerular basement membrane) was detected in 56 patients. Apart from 22 patients with chronic active T-cell mediated rejection and 10 patients with chronic active antibody-mediated rejection, transplant glomerulopathy was also present in some patients diagnosed with borderline changes, drug toxicity, BK nephropathy, IgA, or IF/TA.

DISCUSSION

In the current study, we assessed the pathologic diagnosis of the indication biopsies of renal allografts and evaluated the relationship between histopathological diagnoses and laboratory findings.

At the time of the transplant, the mean age of the recipients and donors was 30.4 ± 10.1 years and 42.3 ± 13.4 years, respectively, representing a young adult population. This allowed elimination of complications associated with renal disease before they became evident, while making the recipients more susceptible to rejection as they were immunologically more active (7). Furthermore, non-compliance with medication tends to be more common in younger transplant recipients due to misconceptions about the side effects of drugs among the general population. This occurred in two patients in our patient group. Young age of a kidney donor is a favorable factor for avoiding alterations that normally occur in the kidneys and ensuring long-term graft survival. Of the relative donors, 12 were siblings, 26 mothers, nine fathers, and five second-degree relatives. Therefore, the mismatch values of 50 patients were three and below, which might indicate that there was no evident problem in the transplanted kidneys in terms of human leukocyte antigen groups.

In their study, Guo et al. analyzed 1500 renal allograft biopsies and found that 213 patients (14.2%) had acute T-cell-associated acute rejection, 36 (2.4%) acute antibody-mediated rejection, 251 (16.7%) chronic T cell-mediated rejection, 45 (3%) chronic antibody-mediated rejection, 106 (7.1%) acute CNI nephrotoxicity, 251 (16.7%) chronic CNI nephrotoxicity, and six (0.4%) had a relapse or new nephropathy (8). The current study examined 92 renal allograft biopsies, which revealed that seven patients (7.6%) developed acute T cell-mediated rejection, 20 patients (21.7%) borderline changes, two patients (2.1%) acute antibody-mediated rejection, 22 patients (23.9%) chronic active T-cell mediated rejection, 10 patients (10.8%) chronic active antibody-mediated rejection, nine patients (9.7%) IF/TA, five patients (5.4%) CNI nephrotoxicity, seven patients (7.6%) BK nephropathy, and nine patients (9.7%) had a relapse or new nephropathy. Another study conducted by El-Zoghby et al. to investigate the reasons for graft loss reported that 12% of their own cases (153 diseases, mainly brain dead organ donors) suffered graft loss due to acute rejection, 56% glomerular disease (recurrent disease, TG, *de novo* disease), 47% interstitial fibrosis/tubular atrophy (IFTA), 16% medical or surgery, and 5% unknown causes (9).

In a recent study, Carlos Arias-Cabrales et al. investigated 495 renal transplant biopsies, of which 28 (5.7%) were not diagnostic. Of the remaining 467 biopsies, 10.3% were normal, 19.6% revealed antibody-mediated changes, 5.9% borderline changes, 8.7% T-cell-mediated rejection, 23.4% IFTA, and 26.5% other diagnoses. Grafts with unfavorable histology (chronic antibody-mediated rejection, moderate-severe IFTA) presented worse survival than those with favorable histology (normal, acute tubular necrosis, mild IFTA) (10).

Concerning the indications for biopsy in the current study, the most frequent cause was rapid deterioration of graft function (42.3%), followed by proteinuria investigation (27.1%), slow deterioration of graft function (29.3%) and primary graft non-function (1.1%). In their study conducted with 329 patients, Sis et al. found that biopsy indications included sudden rapid deterioration of graft function (24%), proteinuria investigation (10%), slow deterioration of graft function (36%), stabilized deterioration of graft function (19%), and primary graft non-function (2%) (11). Although the indications for biopsy are generally known in theory, practical approaches may vary from one center another. Some clinicians may treat cases that are presumed to be caused by rejection after excluding prerenal and postrenal reasons using appropriate drugs without performing renal biopsies. If the medication therapy does not result in improvement, then a biopsy is performed.

Amer et al. investigated the relationship of proteinuria with histology and survival and reported renal biopsy and proteinuria values in the first year as follows: Acute rejection average: 262 ± 389 mg/g (8-1986), IF/TA 229 ± 289 mg/g (2-1931), glomerular pathology 2716 ± 889 mg/g (33-11870), and BK, arteriolar hyalinosis, interstitial nephritis and ATN 239 ± 369 mg/g (24-2738). The values in the glomerular pathology group were found to be statistically higher compared to the other groups (12). In a study conducted by Sun et al., it was found that in patients with proteinuria less than 1g/day, glomerulopathy was the most common reason (36%), acute rejection second (25%), chronic rejection third (14%), and IgA last (3%). On the other hand, proteinuria levels less than 1 to 3.5 g/day was most commonly associated with transplant glomerulopathy (42%), followed by IgA diagnosis (24.4%), chronic rejection (15%), and acute rejection (4.9%). When proteinuria levels of 3.5 g/day and above were examined, it was determined that transplant glomerulopathy was still the most common reason (48%), followed by IgA diagnosis (19%), chronic rejection (5%), and IF/TA (9%), while no acute rejection

was observed. Regardless of histological diagnosis, the most common histological changes observed in patients with proteinuria were interstitial inflammation at a rate of 95.9%, followed by glomerulitis at 70.4%, tubulitis at 46.9%, and intimal arteritis at 14.3% (13).

In the current study, the majority of the patients with proteinuria less than 1000 mg/day were diagnosed with borderline changes or active T cell-mediated rejection. The level of proteinuria observed in the patients diagnosed with interstitial inflammation and tubulitis is also consistent with the findings of previous research in the literature. Patients with BK nephropathy comprised the majority of the other group. In BK nephropathy, cytopathic effects are seen in stage A, tubulointerstitial inflammation in stage B, and tubular atrophy and interstitial fibrosis in stage C (14). Therefore, in BK nephropathy, proteinuria is generally within a non-nephrotic range.

The current study utilized the Banff classification (2009), in which all histopathological components were encoded and graded in detail. The revised Banff classification (2013) does not include antibody-mediated rejection of renal allografts (3). Therefore, the number of chronic or acute antibody rejections may be lower than expected, especially in patients with nephrotic range proteinuria.

The current study revealed that the majority of the patients with proteinuria levels of 3.5 g/day suffered chronic active rejection with glomerular basement membrane changes (including transplant glomerulopathy), FSGS (n=2), MPGN (n=1), and IgA (n=2). In these patients, nephrotic-range proteinuria was expected.

Our study has certain limitations. First, due to its retrospective nature, we were unable to obtain all the patient data. Second, we did not perform a renal biopsy for all patients suspected to have acute rejections at the beginning because this procedure takes a couple of days and it is crucial to start rejection treatment immediately. Third, the biopsy results were evaluated using the Banff 2009 criteria, which may have resulted in overlooking Cd4 negative chronic humoral rejection. Fourth, we were unable to make a comparison between indication biopsies and protocol biopsies due to the unavailability of the latter. Lastly, we were not able to exclude baseline donor factors.

CONCLUSION

The diagnosis of renal allograft biopsies varies due to different approaches of each center to acute kidney dysfunction and proteinuria of renal allograft. It seems that renal biopsy, despite advanced technologies for imaging or detection of biomarker levels, remains an indispensable tool for definitive diagnosis and prediction of survival after renal transplants.

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