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ORIGINAL ARTICLE

Prevalence and causes of graft dysfunction in first 3 months after kidney transplantation in Erbil transplant center

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ABSTRACT

Graft dysfunction after kidney transplantation occur due to different causes. Diagnosis of graft dysfunction is a key component in the management of kidney transplant recipients. The aim of this study was to identify the causes of graft dysfunction in the first 3 months after kidney transplant by kidney biopsy for better graft survival. A total number of 250 patients who underwent renal transplantation at the Erbil teaching center from January 2020 to December 2020 were considered for this study. 50 biopsies were performed due to renal graft dysfunction in the first 3 months post-transplant. Descriptive statistics were analyzed using IBM SPSS Statistics software version 22.0. The biopsy results showed that acute cellular rejection (ACR) was observed in 21 patients (42%), acute interstitial nephritis (AIN) was found in 16 patients (32%), acute tubular necrosis (ATN) was occurred in 9 patients (18%), calcineurin inhibitor toxicity (CNI) was observed in 2 patients (4%), acute humoral rejection (AHR) was found in 1 patient (2%) and thrombotic microangiopathy (TMA) was occurred in 1 patient (2%). As a conclusion, the most important causes of graft dysfunction were ACR, AIN and ATN, respectively. Also, glomerulonephritis, diabetes and hypertension are the most risk factor for ESRD. In addition, the results of this study showed that Anti-HLA cross match can be used as an indicator for predicting the result of transplantation.

Keywords: graft dysfunction, Kidney transplantation, acute cellular rejection, acute interstitial nephritis

INTRODUCTION

Kidney disease is a spectrum of acute and chronic diseases that in some cases leads to the end-stage renal disease (ESRD). In this case, kidney function is irreversibly lost. There are two different treatments for these patients. One of these methods is dialysis and the other is kidney transplantation. Kidney transplantation is the most appropriate treatment for these patients compared to other methods. Kidney transplantation results improved life quality and decreased mortality compared to dialysis (Tonelli et al, 2011). The first successful renal transplant was performed in 1954 in the United States (Doyle et al, 2004). Recipient's immune system recognized donor antigens and results an immunologic reaction called rejection. Despite gradual advances in surgical techniques, progress in immunology and the new immunosuppressive drug introduction remain a major barrier to long-term survival. Kidney biopsy is a confirmatory and direct tool for detecting rejection that can be applied to evaluate the degree and type of rejection (Jeong, 2020).

There are different causes of graft dysfunction after kidney transplantation. Diagnosis and treatment of graft dysfunction is a key component in the management of kidney transplant recipients. Early diagnosis and targeted treatment are important to begin appropriate treatment. Serum creatinine, urine output, and urinary protein are beneficial parameters for postoperative measurement to assist identifying graft dysfunction in the recipient of kidney transplant (Knechtle et al, 2019). Urine output should be measured daily until stabling graft function (Dias et al, 2019). Urine output may be one of the most important and earliest graft dysfunction signs. It has been correlated with graft results. Serum creatinine is a beneficial parameter to detect graft dysfunction and a reliable approach for identifying changes in the function of kidney. In addition, excretion of urine protein should also be monitored and evaluated (Akbari et al, 2014).

The gold standard for the graft dysfunction is biopsy. The outcomes of biopsy lead to change of the treatment in 59% and the diagnosis in 36% of patients (Taheri et al, 2011). As mentioned there are different causes of graft dysfunction such as ejection, infectious and renal diseases, nephritis, necrosis and toxicity (Lemoine et al, 2019). Acute Tubular necrosis (ATN) is one of the most important cause of graft dysfunction. It is mostly the outcome of ischemia- reperfusion injury (Novak et al, 2010). Acute cellular rejection (ACR) is a process of immune-mediated kidney damage. It is detected by eosinophil, mononuclear cell and plasma cell infiltration of tubules and interstitium (Menon et al, 2017). Therefore, a biopsy is useful for the diagnosis of causes of graft dysfunction.

The aim of the study is to identify the causes of graft dysfunction in the first 3 months after kidney transplant by kidney biopsy for better graft survival.

METHODS

Sample collection: A total number of 250 patients who underwent renal transplantation at the Erbil teaching center from January 2020 to December 2020 were considered for this study. 50 biopsies were performed due to renal graft dysfunction in the first 3 months post-transplant. This study was approved by the Regional Ethics Committee of our center, and all patients signed informed consent forms. Sampling method were performed using questionnaire.

Indications in biopsy: The indications for the biopsy were (1) enhancemnet in the serum creatinine (S.cr); (2) proteinuria; (3) decreasing urine output (UOP) or continuous anuria (4) ultrasonography (U/S finding) and (5) panel-reactive antibody (PRA) > 0%.

Statistical analysis: Descriptive statistics were analyzed using IBM SPSS Statistics software version 22.0 (SPSS,

Chicago, IL). For association between variables, chi-square test were used. P-values lower than 0.05 were considered statistically significant. Factor analysis using principle component were performed to find and detect the risk factors among all variables. Reliability was calculated for questionnaire using alpha-cronbach.

RESULTS

The patients included 35 males and 15 females with a mean age of 38.9 ± 11.8 years (mean ± SD). Body mass index (BMI) of 90 % of patients were normal. 98% of recipients underwent dialysis before transplant. Donors included 41 males and 9 females with a mean age of 29.4 ± 6.9 (mean ± SD). The BMI of 98 % of donors were normal. Only 6% of donors were one of relative of recipients (Table 1).

Renal calcineurin inhibitor (CNI) level were measured and 94% of recipients showed therapeutic levels of CNI. Ultrasound (U/S) findings were present for only 16 % of patients. Urinalysis revealed protein in 2% and puss cell in 16 % of recipients. The Anti- human leukocyte antigens (HLAs) crossmatch were observed in 36% of patients. In addition, HLA mismatch was not observed in any of patients.

Also, patients were analyzed and investigated for comorbidities. Hypertension (HTN) was the most common comorbidities in patients (70%). In 16% of patients, HTN were observed with diabetes mellitus (DM). The panel-reactive antibody (PRA) were investigated in patients. In 92% of them, PRA were equal to 0. Only 8 % of patients show PRA of higher 0.

Graft dysfunction was occurred from 2 to 90 days after transplantation with a mean of 42.6 ± 32 days (mean ± SD).

The presentation and indication of graft dysfunction were High S.cr in 44 cases (88%), high S.cr accompanied by anuria in 3 cases (6%), high S.cr accompanied hypertension in 1 case (2%) and high S.cr accompanied by anuria and hypertension in 2 cases (4%).

There are different causes for end-stage renal disease (ESRD). Glomerulonephritis (GN) was the most cause of ESRD in this study which was found in 36 cases (72%). DM caused ESRD in 11 (22%) patients. Each of HTN and polycystic kidney disease (PKD) were causes of ESRD in 2% of cases (Table 2).

The biopsy results showed that acute cellular rejection (ACR) was observed in 21 patients (42%), acute interstitial nephritis (AIN) was found in 16 patients (32%), acute tubular necrosis (ATN) was occurred in 9 patients (18%), calcineurin inhibitor toxicity (CNI) was observed in 2 patients (4%), acute humoral rejection (AHR) was found in 1 patient (2%) and thrombotic microangiopathy (TMA) was occurred in 1 patient (2%) (Table 3).

More than a half of graft dysfunction occurred within the first month after transplantation (28 patients (56%). Within second month after transplantation, graft dysfunction occurred in 10 cases (20%) and the number of patients with graft dysfunction within third month were 12 (24%) (Figure 1). The results of chi square test showed that Anti-HLA cross match was the only significant variable (Table 4). The correlation matrix is presented in Table 5. The biggest negative correlation with biopsy results were related to Anti-HLA cross match (-.759). Cronbach's alpha for 17 variable were 0.256

Table 1. Recipient and donor characteristics.

Variables	Values
Recipient age (years)	38.9 ± 11.8 (20-63)
Recipient sex, f/m (%)	15/35 (30/70)
Recipient BMI, Normal/High (%)	45/5 (90/10)
CNI level, Therapeutic/ high (%)	47/3 (94/6)
U/ S finding (%)	8 (16)
GUE finding (%)	
Negative (%)	41 (82)
Protein (%)	1 (2)
Pus cell (%)	8 (16)
Anti-HLA cross match	18 (36)
HLA mismatch	0 (0)
Dialysis before transplant	49 (98)
Donor sex, F/M (%)	9/41 (18/82)
Donor age (years)	29.4 ± 6.9 (19-65)
Donor BMI, Normal/High (%)	49/1 (98/2)
Related donor (%)	3 (6)
Comorbidities (%)	
HTN (%)	35 (70)
HTN +DM (%)	8 (16)
None (%)	7 (14)
Presentation	
High S.cr	44 (88%)
High S.cr + anuria	3 (6%)
High S.cr +HTN	1 (2%)
High S.cr +HTN + anuria	2 (4%)
PRA (%)	
0 (%)	46 (92)
>0 (%)	4 (8)
Time of Graft Dysfunction (days)	42.6 ± 32 (2-90)

Table 2. The incidence of different causes of ESRD

Causes	Count (%)
DM	11 (22)
GN	36 (72)
HTN	1 (2)
PKD	1 (2)
Others	1 (2)

Table 3. Biopsy results

Results	Count (%)
ACR	21 (42)
AHR	1 (2)
AIN	16 (32)
ATN	9 (18)
CNIT	2 (4)
TMA	1 (2)

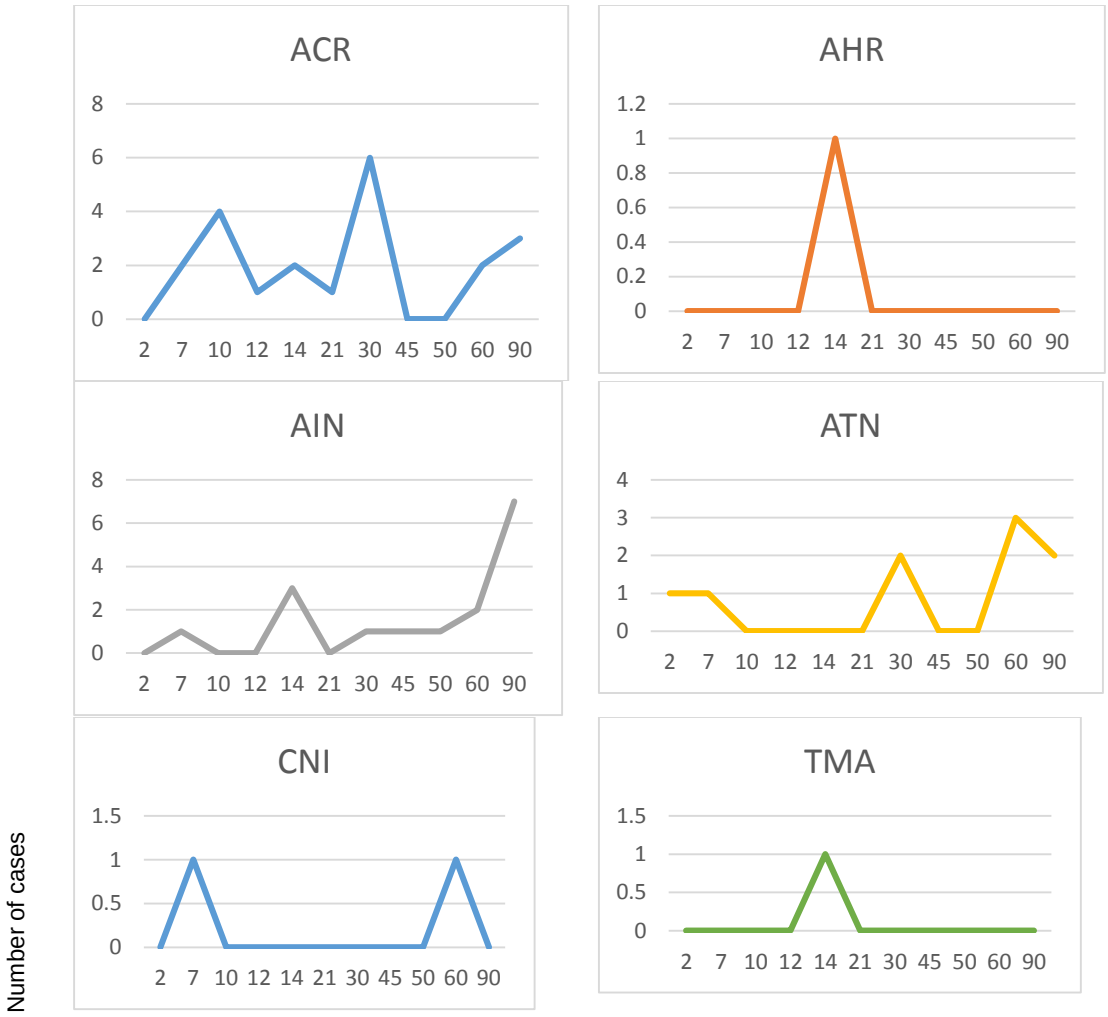

Figure 1. The incidence of different causes of graft dysfunction during 3 month after transplanation

Table 4. The Chi square test of different variables on biopsy results

Variable	χ^2	**P-value**
Recipient age	166.241	0.064
Recipient sex	6.609	0.251
Recipient BMI	1.135	0.951
CNI level	1.294	0.936
U/ S finding	6.272	0.281
GUE finding	6.487	0.773
Anti-HLA cross match	35.946	0.000
Dialysis before transplant	1.409	0.923
Donor sex	4.772	0.444
Donor age	76.682	0.729
Donor BMI	2.168	0.825
Comorbidities	17.287	0.068
PRA	0.599	0.988
Time of Graft Dysfunction	45.262	0.664

Table 5. Correlation matrix of different variables

	Age	Sex	BMI	ESRD	time of GD	Biopsy result	CNI level	u/s finding	GUE finding	Anti-HLA crossmatch	PRA	comorbidities	dialysis	Donor type	Donor Age	Donor gender	Donor BMI	presentation
Age	1.000																	
Sex	-.066	1.000																
BMI	.227	-.073	1.000															
ESRD	-.437	.031	-.238	1.000														
time of GD	.260	-.275	-.127	.110	1.000													
Biopsy result	.009	-.123	-.110	-.014	.169	1.000												
CNI level	.022	.202	-.084	.397	.138	-.144	1.000											
u/s finding	.073	-.190	-.218	.016	.434	.145	.110	1.000										
GUE finding	.045	.290	-.154	.027	.009	.004	.340	-.095	1.000									
Anti-HLA crossmatch	-.179	.055	-.111	-.012	-.177	-.759	.161	-.127	-.007	1.000								
PRA	.176	.129	.147	.042	-.062	-.045	-.075	-.072	.064	.086	1.000							
comorbidities	-.254	-.096	-.018	-.189	.103	.176	-.153	.189	-.018	-.053	-.077	1.000						
dialysis	-.194	-.094	-.048	.020	-.057	-.150	-.036	.062	-.066	.190	-.042	-.087	1.000					
Donor type	.114	.165	.084	-.036	-.096	-.401	.064	-.110	.116	.189	.075	-.079	.036	1.000				
Donor Age	.327	-.145	.065	-.086	.314	-.056	-.041	.148	.028	-.062	-.073	-.237	.011	-.350	1.000			
Donor gender	-.194	.488	.017	-.082	-.097	-.118	-.118	.062	.207	-.026	-.138	.218	-.067	-.101	.135	1.000		
Donor BMI	.012	-.094	-.048	.020	.213	.056	-.036	.062	-.066	-.107	-.042	-.087	-.020	-.565	.737	.305	1.000	
presentation	.003	.045	.188	-.081	-.072	.084	-.083	-.344	.333	-.060	-.097	.089	-.047	.083	.099	.156	-.047	1.000

DISCUSSION

Most of recipients were men (70%) and BMI of most of recipients was normal (90%). Transplant recipients with obesity that are recognized by high BMI, have been represented to experience adverse results more commonly compared to normal-weight transplant recipients. The results of a study showed that transplant recipients with BMI less that eighteen had lower risk of delayed graft dysfunction compared to those with normal weight (Lentine et al, 2012). Therefore, BMI is an important variable that can effect on the result of transplantation.

CNI level in most of patients were in therapeutic levels in this study. CNIs are effective immunosuppressants, but they show wide toxicity features. They need management to ensure being on enough therapeutic dosing to avoid toxicity after kidney transplantation (Fu et al, 2019; Leas et al, 2016).

From the immediate post-operative period, U/S is usually done in renal transplant patients (Poggio et al, 2007). In U/S, the perinephric complications and the internal renal morphology of kidney transplant, can be investigated (Kolofousi et al, 2013). Two-dimensional ultrasound in the evaluation of renal transplants was introduced in the 1970s. But using Doppler approach become a routine practice in the following years. It is a noninvasive and relatively cheap method that can be used for monitoring patients after kidney transplantation. As mentioned U/S finding was positive in 8 cases (16%).

Crossmatching was used for detecting recipients who are likely to develop graft dysfunction or acute vascular rejection. The rejection is an outcome of preformed antibodies to one or more HLA of the donor. A crossmatch include placing the serum of recipient onto donor lymphocytes. If there are donor-specific antibodies, a cytotoxic reaction will occur. In 36% of cases, Anti-HLA crossmatch were positive. The only variable that was significantly different between biopsy results were Anti-HLA crossmatch. Also, the biggest negative correlation was seen between the biopsy results and Anti-HLA crossmatch. Therefore, it is an important and effective variable in this study. There are many approaches for evaluating the immunological barriers like HLA antibodies. Positive anti-HLA crossmatch considered as a prohibition of transplantation and increase the risk of graft dysfunction because of presence of anti-HLA antibodies in the recipients (Mehrotra & Sharma, 2019).

Hypertension was seen in 70% of cases. It is common in renal transplant recipients and ranges from 50% to 80% in recipients. Inadequate control of hypertension results cardiovascular morbidity and mortality and shortened survival (Weir et al, 2015). The results of a study showed that 90.7% of recipients have hypertension (Zhang et al, 2018). Diabetes mellitus is the most important and common cause of end stage renal disease and chronic kidney disease. The cause of ESRD in 22% of cases was DM in this study. Also, 16% of recipients had DM. The results of another study showed that 19.4% of recipients have diabetes (Zhang et al, 2018).

Glomerulonephritis was the most common causes of ESRD in this study. Glomerulonephritis is a heterogeneous class of immunological kidney diseases resulting in differences in the prognosis after kidney transplantation in patients (Lim et al, 2019). Therefore, GN, DM and HTN are the most important factors in the incidence of ESRD.

There are different causes for graft dysfunction. ACR is the result of an immune response of the host against the kidney graft. Commonly patients who experience an enhancement in serum creatinine, show ACR (Menon et al, 2017). As mentioned ACR was observed in 42% of cases in this study. The results of another study showed that ACR was found in 65% of cases (Patil et al, 2018). AIN is an important cause of graft dysfunction and acute renal failure. It can be a result of infection, medications and other factors. The most common causes was reported as delayed hypersensitivity which induced by drug (Raghavan & Eknoyan, 2014). As mentioned it was the cause of graft dysfunction in 32% of cases in this study. ATN is a common syndrome after kidney transplantation. As mentioned, it was observed in 18 % of cases. In a study, the percentage of cases of ATN was 5% (López-Gómez & Rivera, 2008). CNIT, TMA and AHR account for 4%, 2% and 2% of graft dysfunction, respectively.

CONCLUSION

For detecting graft dysfunction, biopsy is useful. As a conclusion, the most important causes of graft dysfunction were ACR, AIN and ATN, respectively. Also, glomerulonephritis, diabetes and hypertension are the most risk factor for ESRD. In addition, the results of this study showed that Anti-HLA cross match can be used as an indicator for predicting the result of transplantation.

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