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Histological changes associated with early and late renal allograft dysfunction in a large three-center transplant program in Iraq

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ABSTRACT

Introduction: Transplantation is the sole viable option for the long-term survival of patients with end-stage renal disease (ESRD) in low-resourced countries.

Objectives: To report the histopathological characteristics of kidney graft dysfunction in a large transplant program of a developing country.

Patients and Methods: Renal transplant biopsies were analyzed by the Banff 2017 classification and subdivided into early (≤1 year) or late (>1 year) post-engraftment periods during the 12 months of 2019.

Results: Here, 290 satisfactory graft biopsies were obtained on 290 patients for graft failure and/or proteinuria. The median age of the recipient was 39 years (interquartile range 28-47), where 77% were male and 5.5% had been previously transplanted and 84% of donors were unrelated. Histological diagnosis was as follow; acute T-cell mediated rejection (A-TCMR; 23.1%), acute tubular necrosis (ATN; 14.8%), interstitial fibrosis and tubular atrophy (IFTA; 11.4%), recurrent or de novo kidney disease (R/DKD; 8.6%), transplant glomerulopathy (TG; 7.6%), calcineurin inhibitor toxicity (CNI; 6.9%), and active antibody-mediated rejection (A-AMR; 8.6%). Early graft dysfunctions were A-TCMR (29%) and ATN (22.4%). Late graft dysfunction included IF/TA, (20.2%), TG (20.2%), R/DRD (17%), and A-TCMR (9.5%). C4d+AMR was equally represented in early (5.6%) and late (6.3%) biopsies.

Conclusion: A-TCMR was the most common cause of early graft dysfunction and was replaced by chronic conditions as the cause of 57.8% of late graft biopsies. The causes of graft dysfunction are not remarkably different from the west and TG will be a major cause of late graft failure in Iraq.

Introduction

Kidney transplantation is the preferred treatment for people with end-stage renal disease (ESRD); however, it is the sole option for the long-term survival of the vast majority of ESRD patients around the world due to restricted availability of dialysis in developing countries (1-3). Over the past four decades, 2-5 years of transplant outcomes have been improved by the availability of calcineurin inhibitors. These drugs decreased the frequency and severity of acute T-cell mediated rejection (A-TCMR (2-4). However, graft survival at 10 years and beyond has not notably improved (3). Interstitial fibrosis and tubular atrophy (IF/TA) are partially the result of ongoing low-grade TCMR but largely of uncertain pathogenesis. Antibody mediated rejection (AMR) might be the leading cause of graft loss within the first five

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years after engraftment. While cell-mediated rejection is preventable and treatable with anti-lymphocyte therapy. There are no current regimens that will prevent antibody development or mitigate their long-term effects on the graft (4).

The first renal transplantation in Iraq was performed in Baghdad in June 1973. Baghdad was the center of Iraqi transplantation until 2003 when the post-war condition forced many surgeons and nephrologists out of the country or into the Kurdish regions of northern Iraq. Northern Iraq currently has approximately 2000 patients living with a kidney transplant (5, 6). The pre-transplant antibody and HLA testing that was available in Baghdad has been effectively re-established in the north but only recently. The continuous availability of testing systems, the adequacy of post-transplant antibody testing and also skill in the interpretation of results, have posed regional issues. The federal government contributes to the expense of immunosuppressive medicine for transplant recipients, however financial constraints are a persistent issue that impacts patient compliance.

Objectives
We undertook this study to collate the diagnoses of transplant biopsies in the early (≤1 year) and the late (>1 year) post-transplant periods to determine the causes of graft dysfunction and how regional differences and availability of treatment might alter outcomes.

Patients and Method
Patients and sample collection
Between January 1st to December 31st, 2019, two hundred ninety patients had 304 kidney allograft biopsies that were satisfactory for evaluation, while fourteen patients had repeated biopsy. We included the first biopsies only in this study (290 biopsies for 290 patients). At least three glomeruli and one artery cross-section were required for a satisfactory biopsy. The patients were divided into two groups; 1) early biopsies obtained ≤ 365 days after transplantation and 2) late biopsies obtained >365 days after transplantation.

Histopathology and diagnostic criteria
All biopsies were studied by light microscopy in 18 serial slices stained with hematoxylin and eosin, periodic acid-Schiff and Masson's trichrome stains. The Jones periodic acid-methenamine silver stains were used on a few occasions to help see alterations in the basement membrane. Electron microscopy was not used to examine any of the samples. On frozen sections, fluorescein-conjugated anti-human IgG, IgM, IgA, C3 and C1q antibodies were employed for direct immunofluorescence (DAKO, Santa Clara, CA). C4d staining was conducted

by indirect immunofluorescence on frozen sections using a monoclonal anti-C4d antibody (Bio-Rad, Inc.).

The histological findings were classified into normal or non-specific changes, borderline cellular rejection (BC), acute TCMR, chronic active TCMR, active AMR, chronic active AMR, acute tubular necrosis (ATN), interstitial fibrosis and tubular atrophy-non-otherwise specified (IFTA-NOS), calcineurin inhibitor (CNI) toxicity, recurrent or de novo kidney disease (R/DKD), BK nephropathy (BKN), or acute pyelonephritis according to the Banff 2017 classification (7,8). After eliminating other causes of double contour glomerular basement membrane (GBM) such as thrombotic microangiopathy and glomerulonephritis, we selected the category of transplant glomerulopathy (TG) diagnosed by the presence of double contours of GBM graded at transplant glomerulopathy (CG) 1b and higher (8). Cases of BKN were confirmed by immunohistochemistry for simian virus-40 (BioSB, Santa Barbara, CA).

Statistical procedures
Biopsy submission forms recorded patient age, gender, time post-transplantation, serum creatinine, and proteinuria level at the time of biopsy, immunosuppressive therapy, donor source, and the existence or lack of donor-specific antibodies (DSA) are all factors to consider. The median and interquartile range (IQR) were used to express the continuous variables of age, time post-transplant (in days), and serum creatinine, the difference between groups tested by Kruskal-Wallis one–way ANOVA on ranks with a post-hoc Dunn's test for pair-wise comparisons. A chi-square or Fisher's exact test was used for between-group comparisons of categorical variables; $P < 0.05$ was considered significant. Data were analysed using IBM SPSS 26 (Armonk, NY).

Results
Patient demographics
Recipients consisted of 290 patients having the characteristics summarized in Table 1. The median patient age was 39 years old, with a range of 12 to 71 years old and an IQR of 28 to 47 years old. Males made up 77.6% of the recipients. All of the donors were alive, with 47 (16.2%) being related and 243 (83.3%) being unrelated. Biopsies were taken on 196 patients less than 365 days after transplantation (early biopsies) and 94 patients more than 365 days after transplantation (late biopsies) from one day to 18 years following transplantation. With an IQR of 1.60-2.55, the median serum creatinine (sCr) was 2.0 mg/dL. There was no significant difference in sCr between patients with early or late biopsies ($P = 0.99$). After excluding non-specific changes and borderline biopsies, no significant differences in sCreat between different

Table 1. Clinical characteristic of recipients

Characteristic	Value
Total number of recipients, n (%)	290 (100)
Median age of recipients (year)	39 (IQR 28-47)
Male, n (%)	225 (77.6)
Living/Deceased donor, n (%)	290/0 (100/0)
Related/Unrelated donor, n (%)	47/243 (16.2/83.8)
Median serum creatinine at biopsy (mg/dL)	2.0 (IQR 1.6-2.6)
Previous transplant, n (%)	16(5.5)
Time of biopsy:	
Early (≤one year) biopsy, n (%)	195 (67.2)
Late (>one year) biopsy, n (%)	95 (32.8)
Maintenance immunosuppressive regimens at biopsy	
CNI (tacrolimus/cyclosporine), MMF, steroid	180 (62)
CNI (tacrolimus/cyclosporine), steroid	110 (37)
Indication for biopsy:	
Primary non function	41 (14.1)
Rapid deterioration of graft function	100 (34.5)
Slow deterioration of graft function	94 (32.4)
Proteinuria	23 (7.9)
Follow up biopsy	19 (6.6)
Other	12 (4.1)
Unknown	1 (0.3)

Abbreviations: Continuous variables of age and serum creatinine and time of biopsy are expressed as median and interquartile range. IQR, interquartile range. CNI; calcineurin inhibitor (tacrolimus/cyclosporine), MMF; mycophenolate mofetil, DSA; Donor-specific antibody.

disease categories were detected ($P = 0.22$). All patients received immunosuppressive therapy, where tacrolimus, mycophenolate mofetil (MMF) and corticosteroids were the most frequent combination (62%). Indications for biopsy included primary non-functioning graft (14.1%), deterioration of graft function (70.3%) and proteinuria

(7.9%). Proteinuria was seen in (6.6%) of early biopsies and (38.9%) of late biopsies ($P < 0.001$).

Pathological results

Figure 1 displays the diagnosis distribution for the year 2019. Acute TCMR was the most common diagnosis, accounting for 23.1%, followed by ATN (14.8 %), IFTA-NOS (11.4 %), TG (7.6%), R/DKD (8.6%) and CNI toxicity (6.9%). Other diagnoses were found in less than 4% including BC, acute TCMR and chronic A-TCMR; since TCMR was diagnosed in 3.8% of biopsies. Biopsies of mixed A-TCMR and AMR were all C4d+ and were included with active AMR. Accordingly C4d+ AMR was identified in 5.9% of biopsies.

In 2018 Banff classification of renal allograft pathology, a C4d- category of AMR is recognized that consists of glomerular and peritubular capillary basement membrane duplication and thickening. This C4d-negative AMR group represented 7.6% of our biopsies, while these patients were reported to nephrologists as TG/C4d-AMR, but were designated as TG for this study.

Table 2 shows the features of the 25 cases of R/DRD. These include a dihydroxyadenine deficiency crystal nephropathy and karyomegalic interstitial nephritis that recurred at 15 and 180 days post-transplantation. Thirteen of the R/DRD cases were diagnosed as the invariably progressive glomerular disease of IgA nephropathy or focal segmental glomerulosclerosis (FSGS) while eleven cases were FSGS that presented at a median of 1460 days (range 730-3650 days) post-transplantation. Notably, three of the eleven cases of FSGS have a TG in addition to the segmental sclerosing lesions of FSGS and striking arteriolar hyalinosis were found in seven FSGS cases (64%).

Table 3 shows the features of the twenty patients diagnosed with CNI toxicity within the first year. CNI
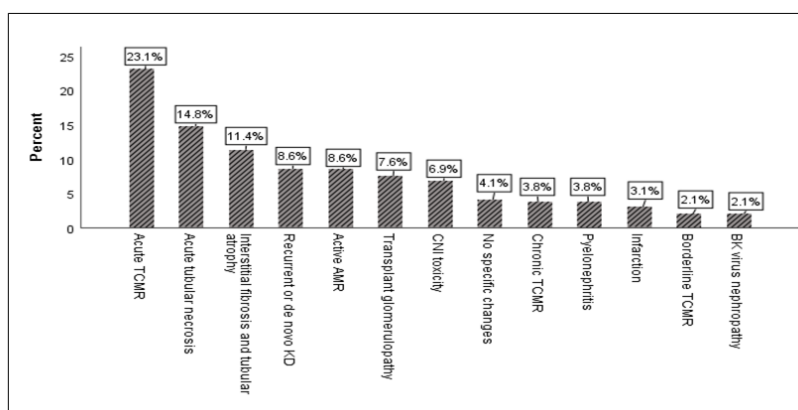

Figure 1. Percentage of patients with diagnosis. Abbreviation: TCMR, T cell-mediated rejection; AMR, antibody-mediated rejection; CNI, Calcineurin inhibitors.

toxicity was diagnosed at a median of 77 days (range 7-210 days) after transplantation based on a TMA. After the first year, CNI toxicity was represented mainly by chronic allograft changes associated with a nodular arteriolar hyalinosis. These chronic changes were attributed to CNI toxicity and were found at a median of 1275 days after transplantation. One patient at 1825 days post-transplantation had an acute TMA and patchy cortical infarction however no TG indicating that the TMA began shortly before the biopsy.

The prevalence of diagnoses in early (≤365 days) and late (>365 days) biopsies are shown in Table 4. Patients with ATN, cortical infarction and no specific changes were almost exclusively found in early biopsies and constituted 75% of these cases including all infarctions; this group was biopsied in the first 60 days post-transplant. Rare cases of ATN of unknown cause were seen late in the first year and even after 12 months.

A-TCMR was more common in early biopsies than late biopsies (29 % versus 9.5 %, respectively; P< 0.001). The median time from transplantation to biopsy for A-TCMR was 60 days (interquartile range 12 to 202 days), while

Table 2. Clinical characteristics of 25 cases of recurrent/de novo kidney disease

Pathological lesions	Number	%	Post-transplant time (days)	sCr (mg/dL)	Proteinuria
FSGS	11	3.7	Median 1460 (range 730-3650)	Median 2 (range 1-3.3)	Present in all cases
IgAN	3	1.03	Median 1095 (range 365-1095)	Median 1.7 (range 1.1-2)	Present in 2 cases only
MCD	1	0.3	365	0.9 mg/dL	Present
MGN	2	0.6	730 and 1095	1.5 mg/dL each	Present in both cases
Myeloma cast nephropathy	1	0.3	240	3.9 mg/dL	Present
AA-amyloidosis	2	0.6	420 and 2555	1.4 mg/dL each	Present in both cases
TMA	3	1.03	Median 120 (range 9-300)	Median 2.6 (range 2.3-2.7)	Not present
DHA deficiency crystal nephropathy	1	0.3	15	1.7	Not present
Karyomegalic interstitial nephritis	1	0.3	180	1.7	Not present

Abbreviations: TMA, Thrombotic microangiopathy; sCr, serum creatinine; MCD, minimal change disease; MGN, Membranous glomerulonephritis; IgAN, IgA Nephropathy; FSGS, Focal segmental Glomerulosclerosis; DHA, dihydroxyadenine.

Table 3. Patients' features with CNI toxicity

Patient No.	Age (y)	Donor relation	Period of transplantation/days	Pathological diagnosis	Proteinuria	Banff score		
						IF/TA	CG	AH
1	64	Unrelated	20	Acute tubular necrosis	Negative	0	0	0
2	24	Unrelated	45	Acute tubular necrosis	Negative	0	0	1
3	28	Unrelated	7	TMA	Negative	0	0	1
4	38	Unrelated	20	TMA	Positive	0	0	0
5	45	Unrelated	60	TMA	Negative	0	0	0
6	42	Related	60	TMA	Negative	0	0	0
7	43	Unrelated	65	TMA	Negative	0	0	0
8	35	Related	90	TMA	Negative	0	0	1
9	28	Unrelated	150	TMA	Negative	1	0	2
10	41	Unrelated	180	TMA	Negative	1	0	3
11	16	Related	180	TMA	Negative	1	0	0
12	40	Related	210	TMA	Negative	2	0	0
13	19	Related	480	Peripheral arteriolar hyalinosis	Negative	1	0	2
14	70	Unrelated	910	Peripheral arteriolar hyalinosis	Negative	3	0	3
15	24	Unrelated	1095	Peripheral arteriolar hyalinosis	Negative	2	0	3
16	46	Unrelated	1275	Peripheral arteriolar hyalinosis	Negative	1	0	3
17	62	Unrelated	1460	Peripheral arteriolar hyalinosis	Positive	2	0	2
18	50	Related	1825	Thrombotic microangiopathy	Negative	1	0	0
19	30	Unrelated	2555	Peripheral arteriolar hyalinosis	Negative	1	0	3
20	42	Unrelated	4015	Peripheral arteriolar hyalinosis	Positive	2	3	3

Abbreviation: TMA, thrombotic microangiopathy; IF/TA, interstitial fibrosis and tubular atrophy; CG, transplant glomerulopathy score; AH, arteriolar hyalinosis.

Table 4. Pathological diagnosis in relation to time of transplantation

Pathological lesions	Early biopsies ≤1 year (n = 196)	Late biopsies >1 year (n = 94)	*P* value
Acute TCMR	57 (29%)	9 (9.5%)	0.00008
AMR (C4d+AMR)	11 (5.6%)	6 (6.3%)	0.795
Borderline rejection	5 (2.5%)	1 (1%)	0.668
Mixed rejection	6 (3%)	2 (2.1%)	1.000
Chronic TCMR	5 (2.5%)	6 (6.3%)	0.185
TG (C4d-AMR)	3 (1.5%)	19 (20.2%)	0.0001
IF/TA NOS	13 (6.6%)	19 (20.2%)	0.001
ATN	44 (22.4%)	3 (3.1)	0.00002
CNI toxicity	11 (5.6%)	9 (9.5%)	0.224
No specific changes	12 (6.1%)	0 (0%)	0.011
Acute pyelonephritis	9 (4.5%)	1 (10%)	0.175
Recurrent/De novo kidney disease	8 (4%)	16 (17%)	0.0003
BK nephropathy	4 (2.0%)	2 (2.1%)	1.000
Number of recipients			**Total**
Non-adherent	8	11	19
Adherent	141	39	180
Unknown	46	45	91

Abbreviations: TCMR, T-cell mediated rejection; AMR, Antibody mediated rejection; TG, Transplant glomerulopathy; IF/TA NOS, Interstitial fibrosis and tubular atrophy, non-otherwise specified; ATN, Acute tubular necrosis; CNI, Calcineurin inhibitors.

fourteen cases (20%) were detected sporadically between one and ten years following transplantation. The A-TCMR was modest, with 75% having grade I tubulointerstitial disease and 22.4 % having grade II tubulointerstitial disease with vascular involvement (Table 5). Early and late biopsies had almost similar percentages of active AMR and chronic TCMR. Chronic TCMR was not seen after 1400 days (3.8 years) where active AMR was observed with little change at a frequency of approximately 3% of biopsies over a period of 3,650 days.

Transplant glomerulopathy and interstitial fibrosis/tubular atrophy, were found mainly in late biopsies or late in the first year post-transplantation. Two IF/TA biopsies have 3+ interstitial fibrosis at 14 and 90 days that was thought to have been donor-related. The earliest time for the identification of TG in the first year was 300 days in one case.

Discussion

This study included only biopsies from the year 2019.

Table 5. Grades of acute cell-mediated rejections in the biopsy series

Type of rejection	Number	%
Acute TCMR	67	100
Grade IA	29	43.3
Grade IB	21	31.3
Grade IIA	9	13.4
Grade IIB	6	9.0
Grade III	2	3.0

Abbreviation: TCMR, T-cell mediated rejection.

The renal biopsy service is centralized and has been the repository for all biopsies in the region since 2009. The number and proportion of transplant biopsies have increased over the past five years, however we have not seen any significant changes in the major categories for diagnosis. This suggests consistency in the clinical criteria that are applied when performing a biopsy and that the year 2019 is representative of the region's multi-year experience.

The characteristic clinical features of recipients are identical to those seen in prior Iraqi trials and those reported from nearby countries (9-11). In this study, transplanted kidneys were all from living donors. (Kidney donation in Iraq is constrained by religious and social challenges) (5).

Despite a religious fatwa issued in 1986 (the Amman declaration) that allows for the recovery and transplantation of deceased donor organs, only Iran and to a lesser extent Turkey have programs that collect and effectively distribute kidneys (12,13). The public opinions about transplantation also affect related donor transplants and only represent 16.2% of the 2019 grafts.

Acute TCMR is the most frequently diagnosed cause of graft dysfunction in our study (23%) especially in below one-year biopsies. This is more than what is reported in a Pakistani study and western countries (2, 11-14). This can be a result of non-adherence to the immunosuppression regimen; since 6.5% of our patients are non-compliant to their drug regime. Fourteen cases that demonstrated interstitial infiltration in non-sclerotic and sclerotic cortex with tubulitis (excluding the severely atrophic

case) were diagnosed as chronic active TCMR (3.6%). The significance of addressing histological features as chronic active TCMR is that it is related to chronic under-immunosuppression and is a sign of injured renal tissue (7,8).

There were two cases of hyper-acute rejection (0.6%); both patients were sensitized patients transplanted for a second time with positive DSA (15).

The second group of AMR was the active and active chronic AMR. Here, all biopsies showing C4d staining (including mixed rejection) form 7.6% of biopsies. This is less than western countries and more than a Pakistani study (2,11). This variation is related to the availability of diagnostic tests as DSA; however, not all our patients have a DSA test either due to the lack of availability of the test or its cost. In the category of chronic AMR, we include cases that showed TG as double contouring of >25% of GBM, which can be seen by light microscopy [transplant glomerulopathy (CG) grade Ib and above] (7) with negative C4d staining, after excluding hepatitis C virus infection, autoimmunity and thrombotic microangiopathy. Transplant glomerulopathy is accepted as the principal histologic phenotype of chronic AMR and indicates a sustained endothelial injury. The overall incidence of TG increases with time post-transplantation in our study; while TG was seen in 19.6% of late biopsies versus 1.9% in early biopsies (*P*<0.0001) (2,16).

In late biopsies, the most common cause of graft dysfunction was IF/TA-NOS (, which replaced the older term chronic allograft nephropathy in Banff. Interstitial fibrosis/tubular atrophy is a descriptive term and does not explain the underlying mechanism (17). Some studies have shown that it is a sequel of tissue injury caused by acute rejection. Interstitial fibrosis/tubular atrophy is also a common finding in antibody-mediated injury and the HLA antibodies are pathological factors. Other studies indicate the role of macrophages in chronic allograft injury as M1 macrophages exacerbate renal cell damages by inflammation and M2 macrophages promote fibrosis by their anti-inflammatory effect (18,19).

Cases of R/DKD constitute about (7.5%) of total cases without significant difference between the early and late biopsies group (*P* = 0.350), which is compatible with other studies (2,14). FSGS was the most common and where glomerulonephritis represents 14% of causes of ESRD in our community with FSGS representing 41% (20).

Conclusion

The study defines the causes of graft dysfunction based on histology of indicated biopsies in early and late period post-transplantation. The cause of graft dysfunction varies with time while acute cellular rejection was the most common cause of graft dysfunction. It peaked in

the first year following the transplant, since IF/TA-NOS and TG a histological feature of chronic AMR accounted for 11.4% and 7.6%, respectively. These occurred mainly after the first year of transplantation. Unfortunately, renal allograft pathology services rely heavily on light and immunofluorescence microscopy and better tools such as electron microscopy or molecular analysis are required.

Limitations of the study

Limitations of the study included the lack of accurate centralized database of renal transplant patients as well as non-availability of electron microscopy.

Authors' contribution

Study design and concepts by AAA. Data collection by AAA, SEA and DAS. Data analysis and the first draft of the manuscript by AAA. All authors approved the final draft.

Availability of data and materials

The Shorsh hospital pathology department has compiled data and computations, which will be made available upon request.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The ethical committee of the faculty of medical sciences at the University of Sulaimani (reference#62) approved this work. The study was carried out in accordance with the Declaration of Helsinki. A review of existing medical and pathology records was conducted as part of the study. It did not necessitate any further patient involvement or informed consent. This study was extracted from Ph.D., thesis of kidney transplant pathology at the department of pathology at University of Sulaimani (Thesis#11N/29). Besides ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by authors.

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