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Significance of renal Allograft Biopsy in correlation with its survival, clinic-biochemical panels

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ABSTRACT— Renal transplantation is the treatment of choice for most patients with end stage renal disease., renal biopsy is the gold standard to assess the causes of renal allograft dysfunction. This study was designed to evaluate and designate renal lesions according to Banff schema and to determine the safety and efficacy of the practice of renal allograft biopsy and verify its impact on the management of kidney transplant patients presenting with graft dysfunction and its correlation with graft survival and clinic-biochemical parameters. In this cross-sectional study, all renal allograft biopsies obtained from renal transplant patients at Baghdad teaching hospital in Iraq during 2013-2014 were studied. Evaluations were made according to the Banff classification 2009. Clinical and biochemical data and pathological reports were collected and analyzed using SPSS analysis method. We studied 55 renal allograft biopsies of 55 adult patients (61.8% males, 38.2%females) mean age was 32.4 years, performed in the medical city complex from February 2013 to May 2014. All the biopsies were performed with a guidance of ultrasound. The procedure, complications, histological diagnoses and impact of the biopsy data on patients' management were recorded. Thirty percent of the biopsies were performed in the first 12 months post-transplantation and 70 % were performed after the 60th month. Adequate biopsy was achieved in 90.9% of the patients. Acute rejection was diagnosed in 36.4% of the biopsies and chronic allograft Nephropathy in 41%, and they were the most common histological patterns in the study. The commonest causes of graft dysfunction after kidney transplant were IF/TA. Living donors were found to be important sources for kidney transplantation in Iraq. Allograft biopsy was a useful and a relatively safe tool for the diagnosis of acute and chronic graft dysfunction in our experience, since there were no major complications and minor complications were rare and with negligible consequences. This procedure using 16-gauge needles also is efficient, as the majority of samples were adequate for diagnostic purposes. None specified symptoms allow for clear differentiation between stable transplants with normal histology and stable transplants with subclinical rejection. Therefore, the protocol allograft biopsy currently remains the preferred tool to screen for subclinical transplant injury. A protocol biopsy is an excellent method for the early diagnosis of disorders in the transplanted kidney and to monitor the effects of immunosuppression. The protocol biopsy, followed by appropriate treatment, promotes preservation of kidney allograft function and therefore improves long-term graft survival.

KEYWORDS: renal Allograft Biopsy, clinic-biochemical panels, protocol biopsy

1. INTRODUCTION

End stage renal disease affects the lives of disproportionate amount of people around the world; in 2012 more than 2.35 millions patients received renal replacement therapy.

In the early 1960, drug therapy for kidney allograft recipients consisted of azathioprine and corticosteroid,

and acute rejection episodes was common with fever and graft tenderness [1]. Clinical picture has virtually disappeared with introduction of immunosuppression by means of powerful CNI in the early 1980s and better immunologic matching of recipient and donor change the character of acute rejection Although the rise in serum creatinine points towards reject ion, subclinical rejection may be apparent only on biopsy of organs and the absence of renal dysfunction can lead to damage the allograft [2]. Allograft (allogeneic graft): A graft between non identical members of the same species. Examples include grafts between unrelated or related nonidentical humans; Rejection occurs by lymphocytes reactive to alloantigens on the graft (i.e., alloresponse) [3].

The histological finding on biopsy influence the progression an the choice of therapy Rejection can be:
Hyper acute (occurring within minutes)
Acute (occurring within days to weeks)
Late acute (occurring after 3 months)
Chronic (months to years
Banff Classification of Renal Allograft Pathology as following [5- 7]

1. Normal
2. Antibody mediated rejection
Documentation of circulating anti-donor, and C4d or allograft pathology
C4d deposition without morphologic evidence of active rejection (C4d+)
Presence of circulating antidonor antibodies, no signs of acute or chronic T
Cell-mediated or antibody-mediated rejection

Acute antibody-mediated rejection
C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as:
I. ATN-like minimal inflammation
II. Capillary and glomerular inflammation and/or thromboses
III. Arterial - v3

Chronic active antibody mediated rejection
C4d+, presence of circulating antidonor antibodies, morphologic evidence of tissue injury such as:
Glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening
3. Borderline changes
Suspicious for acute T-cell mediated rejection
No intimal arteritis but foci or tubulitis (t1, t2 or t3 with i0 or i1)
4. T cell mediated rejection
Acute T cell mediated rejection
Type
IA Interstitial infiltration and moderate tubulitis (i2 or i3 and t2)
IB Interstitial infiltration and severe tubulitis (i2 or i3 and t3)
IIA Mild to moderate intimal arteritis (v1)
IIB Severe intimal arteritis (v2)
III Transmural arteritis and/or fibrinoid change and/or smooth muscle necrosis

Chronic active T cell mediated rejection
“Chronic allograft arteriopathy”

Arterial fibrosis with mononuclear cell infiltration in fibrosis
5. Interstitial fibrosis and tubular atrophy, no specific etiology (formerly known as CAN)
Grade
I Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
II Moderate interstitial fibrosis and tubular atrophy (26%-50% of cortical area)
III Severe interstitial fibrosis and tubular atrophy (>50%) cortical area

6. Changes thought not due to rejecton - either acute or chronic
It can be classified according to pathophysiological changes (cellular, interstitial, vascular, antibody mediated) [5].

Severity (extent of histological inflammation and injury as scored and graded by means of the Banff schema
The immunologic threat to renal graft begins before transplantation and a rise from the systemic effects of donor brain death or perioperative ischemia –reperfusion injury [6].

Ischemia followed by reperfusion up regulate the expression of HLA antigens by the graft and causes release of cascades of cytokine and chemokines and adhesion molecules within graft [7].

Antibody that can mediate rejection include
Those against the HLA molecules, endothelial cell antigens, ABO blood group antigens on endothelial cells and red cells.

Most recipients had no antibody against HLA molecules before transplantation unless they are sensitizes by exposure to allo antigens through pregnancy, blood transfusion, or previous transplantation [8- 9].

Hyper acute rejection
Rejection of renal allograft that occur almost immediately after release of vascular cross clamps, the kidneys become flaccid and mottled reflecting the deposition of antibody against the HLA antigens expressed on the endothelium of the glomeruli and micro vasculature, Activation of the classic complements cascades within graft is followed by endothelial necrosis, platelets depositions and local coagulations [8].

Improvement of cross matching technique that include better detect donor specific antibody (DSA) before surgery have largely eliminated this problems.

Acute antibody mediated rejection
Antibody mediated rejection begins within days after transplantation or within weeks if anti lymphocyte antibody was given. The main features is rapid graft dysfunction due to inflammation main target of these recall antibody Are MHC antigen displayed by the endothelium, early diagnosis and treatment are essential for salvaging graft undergoing acute antibody mediated rejection [9], [10], treatment involved removal antibody by plasmaphresis or immunadsorption, high dose pulses of corticosteroid, I V IG, anti-proliferative therapy [11], [12].

Supplementary therapy
Include rituximab or anti lymphocyte antibody if there is concurrent T cell mediated rejection, this treatment so useful if use as prophylaxis to highly sensitized or ABO mismatched recipient's, Eculizumab (monoclonal antibody inhibit the cleavages of corticosteroid, Bortezomib (plasma cell inhibitor) can be

used also in AMR [13]

Detection of potentially harmful antibody before transplantation should prompt a search for an alternative donor or an aggressive approach to post transplantation management [14]

T cell mediated rejection most common form of acute allograft rejection is initiated when donor alloantigen are presented to the T lymphocyte of the recipients by antigen presenting cells immature dendritic cells within graft carry donor antigen from transplanted organs to the recipient's draining lymph node and spleen during their journey [10] antigen mature to APC, recipient.

The APC then home to lymphoid organs, where they stimulate the recipient's T cells [14], and these T cells differentiate into various subgroups and return to the graft when they take part in destroying the transplanted organ [15].

Kidney biopsy

There are diagnostic criteria on microscopic evaluation of donor biopsy for determination of post-transplant dysfunction in allograft. Found an association between biopsies with more than 20% glomerulosclerosis and more DGF, higher creatinine levels at 1 year and increased graft loss [17] According to donor characteristics such as age (the most potent predictor of long-term outcome) [18] suggested that donor kidneys with less than 6% glomerulosclerosis were associated with better graft outcomes. Vascular changes and tubulointerstitial findings may also be associated with early and late graft outcomes.

Biopsy performed for specific clinical indication or part of surveillance program (protocol biopsy) [19]. An indicated biopsy is one that is prompted by the change in the patient clinical condition and or laboratory parameter. A protocol biopsy is one obtained at pre-defined interval post transplantation, in both cases, biopsy obtained to found histological changes prompting treatment to improve outcome.

Prior to the procedure, all patients underwent blood and coagulation tests, 7 day washouts of oral anticoagulants and antiplatelet agents, and suspension of heparin 24 hours before. After the procedure no routine renal ultrasounds were performed, unless complications were suspected [20].

Although serum creatinine has many limitations for estimating GFR, an unexplained rise in serum creatinine is generally indicative for decline of GFR, fluctuation in creatinine can result from normal lab or physiology variability [21].

Hence only persistent rise that is outside this normal but poorly defined range is clinically relevant. At least one study suggested that persistent 30%rise in the serum creatinine was an excellent predictor of subsequent graft failure.

Causes of acute, reversible decline of GFR should be ruled out including dehydration, urinary obstruction or acute CNI toxicity before biopsy is performed [22].

Biopsy of delayed graft function (DGF)

Observational studies showed that incidence of acute rejection during DGF is higher than patients without DGF [23].

Number of studies have revealed variable frequency of these rejection, [24] reported that subclinical and

border line rejection 21% -25% were noticed respectively in biopsies performed in the first week after transplantation.

[25] have been reported presence of a clinically quiet rejection in more than 50% of protocol biopsy after 1 month post transplantation. Also report an evidence that protocol biopsy of stable renal function are valuable for diagnose chronic allograft nephropathy before deterioration of graft function.

Some centers have performed protocol biopsies as an attempt to diagnose CAN at an earlier stage. In these studies, the timing of histological evaluation has been targeted during the first two years after transplant. Nevertheless, CAN was a frequent finding in all of the studies, ranging between 25 and 70 % [26- 28]. In studies of sequential protocol biopsies it has been observed that the incidence and severity of CAN is time dependent. [28] found that 42%of cases display CAN at 3 months post transplantation,

1.1 AIM OF STUDY

Is to find out types, causes, rates of complications following renal transplantation in our practice comparing our results with other studies and suggesting measures to prevent that and to find any correlation between the presenting symptoms, survival of the patients with renal histopathological pattern and serum creatinine level and blood urea.

2. PATIENTS AND METHODS

Fifty five patients (34 male, 21 female) with renal transplantation were included in this study. There were 2 groups of patients: Retrospective arm (n=41), Prospective arm (n=14). All biopsies were operated in our center and performed and supervised by the same operator under ultrasound guide, all the biopsy specimens were routinely fixed in 10% formalin.

Data analysis was computer assisted using SPSS 18 (Statistical Package for Social Sciences). Allograft biopsies were classified according to the Banff 2009 system, 5 Cases with more than one diagnoses were categorized according to the main diagnosis.

Continuous variable presented as mean ± SD and discrete variable presented as number (%). Correlations examined using Spearman's rank correlation coefficients. P values of ≤ 0.05 were considered significant.

To be retrospective in order to documents as much as possible of the demographic and characteristics of the patients and potential early and late complications.

We prepared a data sheet containing all necessary information and also we built up a biopsy based strategy.

Patients with transplanted kidney who agreed to participate were recruited in this study regardless their age and gender. Data of the patients were kept confidentially and didn't disclosed to non-authorized individuals, and these data were merely used for the purposes of this study., Patients were admitted to hospital day of biopsy and were discharged 24 hours after procedure.

Upon arrival to our unit the patients were thoroughly assessed clinically noting the duration of transplant and any comorbidities or heritable conditions, coagulation parameter peripheral blood count, blood pressures were assessed too.

Patients with a known coagulation disorder or patients on warfarin, aspirin, clopidogrel who were not

allowed to stop these medications before biopsy were excluded from our program.

Patients with systolic blood pressure >160 mmhg were treated with antihypertensive until the BP back under 160, if this is not reached the biopsy was postponed.

Before biopsy, patient asked to void, renal ultrasound preceded the actual biopsy, and all patients were biopsied in supine position using a 16 gauge needle with a spring loaded gun (Bard) under real time ultra sound guidance.

2 cores were taken per procedure, from upper and lower pole s of the kidney, in case of pyelocalceal dilatation with presumed obstruction the biopsy was deferred after biopsy, the patients were instructed to remain supine during next 4 hours bed rest, after that the patients could get up for using toilet or for eating but remained in their bed for rest of observation period.

Vital signs were checked every 15 minutes for 2 hours, every hour for 4 hours, every 2 hours for 6 hours and every 4 hours after that, all voided urine was inspected for macroscopic hematuria.

Each patient had an outpatient follow up visit with nephrologist in our center within 1-4 weeks post biopsy
In addition we examined the histology report for assessment of adequacy of tissue samples; specimen adequacy of renal allograft biopsy is defined according to the Banff classification. An adequate sample is a biopsy with 10 or more glomeruli and at least 2 arteries was seen in 50 patients (90.9%). Total number of the patients was 55 male 34(61.8%) and female 21 (38.8%). The studies involved a prospective group (41) and a retrospective group (14).

The lightest weight in the study was 32 Kg (1.8%) and heaviest one was 82 kg (1.8%).

The youngest patient was a boy of 15 years and oldest was man of 65 years .5 patients was HCV positive (9.1%), 4 patients was HBV positive (7.3%). 4 patients (7.3%) had a second transplant after failure of the previous graft, 7 patients were hypertensive (12.7%), 2 patients was diabetics (3.6%), 11 patients (20%) had been received a kidney from related donor, (80%) received from unrelated ones. all donors were living ones.2 patients suffered from BK nephropathy (3.6%) and only 3 patients suffered from CMV infection (5.5%).

Graft survival less than 1 year was noted in 18 patients (32%). azathioprine were taken by 3 patients (5.5%), 30 patients were continued on tacrolimus (54%). Two patients maintained on sirolimus (3.6%). 46 patients (83.6%) take MMF.15 patients take cyclosporine (27.3%).

Steroid free regimen not adopted in a large scale in our practice (1.8%).

Oldest graft transplanted included in our study was at 1999

Histologically 23 patients their renal biopsy revealed IFTA (41%). 3 biopsies revealed pyelonephritis, four patients reported a viral infection which is not specified what sort of viral infection is that, nine patients showed antibody mediated rejection (AMR)(16.4%).

11 biopsies revealed a cellular rejection (20%). Two biopsies showed a picture of CNI toxicity (3.6%), and one only (1.8%) showed a recurrent of previous initial disease (IGA nephropathy).2 biopsies showed

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inconclusive finding (3.6%).12 patients (21.8%) presenting to medical attention with symptoms suggestive for graft dysfunction (e.g.: generalized fatigue, decreased urine output).78.2% of patients included in the study were free from symptoms.

No serious complications arise after graft biopsy apart from 5(9.1%) patients suffered from minor complication (pain, mild macroscopic hematuria)

A resistive index of more than or equal to 0.7 was considered elevated and considered correlated with an elevated serum creatinine level of more than or equal to 1.5mg/dl.in our study we found that only 7.3%of the patients included had a RI of less than 7. This study that enrolled 55 transplant recipients patients of variable duration were included in the study, 97 males and 65 females and their age range from 20 to 60 years old, with male to female ratio 1.4 :1.

Duration since transplantation time (months)	No.
<1 month	3
<12	6
12-24	30
>24	16

TCMR distribution among transplanted patients(1)

		Frequency	Percent	Valid Percent	Cumulative Percent
	Not TCMR	44	80.0	80.0	80.0
	TCMR	11	20.0	20.0	100.0
	Total	55	100.0	100.0	

ABMR distribution among transplanted patients(2)

		Frequency	Percent	Valid Percent	Cumulative Percent
NOT ABMR		46	83.6	83.6	83.6
		9	16.4	16.4	100.0
ABMR	Total	55	100.0	100.0	

Chronic allograft failure distribution among transplanted patients(3)

		Frequency	Percent	Valid Percent	Cumulative Percent
	Not CAN	32	58.2	58.2	58.2

CAN	23	41.8	41.8	100.0
Total	55	100.0	100.0	

3. DISCUSSION

Kidney allograft loss in the first 10 years after transplantation is a major problem for both patients and physicians. Knowing the etiologies of allograft dysfunction makes the physicians manage patients with renal dysfunction in a better way. Based on our knowledge this is a second study on kidney allograft diseases were performed in Iraq. In our study, based on Banff classification we found that the commonest pathology in Iraqi renal allograft biopsies were IF/TA (41.8%) followed by cellular rejection (T cell mediated rejection) (TCMR) (20%) and humeral rejection (16.4%). Both of them were seen more in men (34%) than women (21%) this is consistent with Seron et al who reported that 42% of cases display CAN at a 3 months biopsy [28] also consistent with [30] which showed that CAN is found in (38%) but inconsistent with TCMR (38%)and ABMR (6%). Moreover, [31] observed CAN in 30.4% of stable allografts in pediatric patients at about 100 days after living-related (LR) renal transplantation. Our results inconsistent with Iranian study done at Isfahan which showed that the commonest pathologic findings in patients with cadaveric, living related and living unrelated donors were ATN (81.2%) followed by IF/TA (NOS) (37.5%) [32].

In an observational prospective cohort study of 1307 consecutive nonselected patients who underwent ABO-compatible, complement-dependent cytotoxicity-negative cross match kidney transplantation in Paris (2000–2010). Participants underwent prospective screening biopsies at 1 year post-transplant, 727 (73%) patients without rejection, 132 (13%) patients with subclinical T cell-mediated rejection (TCMR), and 142 (14%) patients with subclinical antibody mediated rejection(ABMR) [33]. Results was not consistent with our result as most of biopsies underwent in our research revealed rejection process (78%).

[34] showed that hepatitis c infection eventually result in significant increase in the incidence of DGF and ABMR but in our study showed that no significant correlation between graft survival and infection with hepatitis B or C except with pyelonephritis.

Living donors are the only donors and the commonest pathologic process leading to renal allograft dysfunction was IF/TA in living unrelated donors. Many studies described the usefulness of renal allograft biopsies and its safety. The adequacy of kidney allograft biopsies had been addressed by many studies and by the Banff criteria. [35] conducted a study that included 1171 biopsies, and 49% of the biopsies were inadequate especially with the use of the 18 gauge needle. In our study 9.1% of the biopsies were inadequate. In terms of containing less than seven glomeruli or containing only one vessel. We used both 18 and 16 gauge needles, but the Difference in the yield of each one of them was not studied.

Kidney allograft biopsies as an outpatient procedure in transplant has been reported Small series, and mainly in pediatric patients. [35] studied the ambulant graft biopsy in adult renal transplant patients.in the current study, all the biopsies were performed as a day case procedure; no patient needed hospitalization. This is inconsistent with the rate of hospitalization in the German study (2%).

Regarding the safety of the procedure, we had one patient who developed sub capsular hematoma (<2 cm × 2 cm) as revealed with ultrasound, and another two who developed microscopic hematuria. Another two developed macroscopic hematuria, All those patients were managed conservatively and this is corresponding to (9.1%) who suffered from this minor complications which is more than what is seen in

Irina study (2.7%) [36].

Future studies may suggest a stronger association between type of donor and pathologic findings in renal allograft biopsies. Presence of HCV infection and its relationship with renal transplantation survival rate is still controversial., [37] showed that graft and patient survival in HCV positives and negatives recipients have been reported to be equal .as our study showed no significant correlation between infection with hepatitis C and graft survival.

Another study of BK viruria in renal transplanted recipients by [38] revealed That polyomaviruses (BK and JC) were very prevalent among Iranian transplanted kidney biopsies in the first 2 years after transplantation which is not seen in our practice (only 2 patients were affected by BK induced nephropathy during the first 2 years post transplantation).

A study in Bahrain, 10 year renal allograft biopsies were evaluated for lesions. While the lesions were 34.6% acute rejection and 42.2% chronic rejection, 23.2% of all biopsies did not show any pathologic evidences of rejection. Most histopathology findings Were IF/TA (26.9%) which is inconsistent with our result which is much higher (41.8%) of cases involved had IF/TA [39].

In another study in Oxford Transplantation Center, 20% of cases were not associated with Rejection which is away from the result we obtained (78.2%) [40]. Comparing with these centers, Bahrain and Iran were more similar in biopsy results and IF/TA NOS was the commonest pathologic finding in both centers. Which is similar to our center result, therefore; long-term follow-up of patients with transplanted kidney will show the outcome and survival duration of allograft kidney. In our study, we did not follow patients for a long period of time and future studies with stronger assessment of long-term pathologic results are required.

Doppler ultrasonography is noninvasive diagnostic techniques that would reliably predict the outcome of transplantation and kidney allograft function after revascularization of the transplanted kidney. It is not only a useful tool for early evaluation of the kidney allograft vasculature and function but also is a reliable noninvasive tool readily available for identifying patients who may benefit from kidney allograft revascularization and for assessing the effectiveness of the procedure [41].

Increased resistive index (RI) as measured by duplex Doppler in the intrarenal arteries may occur in renal parenchymal disease but its, though high sensitive in indicating dysfunction, a poor indicator of the type of parenchymal diseases for example, regarding transplanted kidney, increased resistive index can occur in acute rejection but also in acute tubular necrosis and cyclosporine toxicity, renal vein thrombosis, acute pyelonephritis and obstruction. Rejection tends to produce higher levels than other pathologies [41]. While in case of transplant renal artery stenosis there is decrease in the value of RI (Resistive Index) of less than 0.52 is noticed. The mean resistive index was (55.5), In two studies done in Iran, the mean values of the RI for kidney transplant patients were 0.61±0.08 and (0.57± 0.55), which were similar to some extent to the values determined in our assessment which is (55.5 ± .96). In a recent study by [42], the mean RI were reported to be 0.69 ± 0.06,10 finding close to the range of our finding [43].

continuous steroid therapy was not required to prevent progressive injury or preservation of graft function in patients without biopsy-proven acute rejection but our study showed that only one patient maintained with steroid free regimen.

We report a low incidence (5.5 %) and milder form of cytomegalovirus disease at our center. Use of universal cytomegalovirus prophylaxis was associated with a low incidence and milder form of the disease. Incidence of CMV disease was similar to [44].

In current series, the incidence of minor bleeding complications was also very low (5.6%) comparable to what is reported in our study (9.1%) [45].

4. CONCLUSION

In summary, in our study, we have witnessed that IFTA occurred even after short period post transplantation and it's the most predominant type. These conditions can be diagnosed before the appearance of the symptoms. Proactive attitude toward the diagnosis of the conditions responsible for graft dysfunction may contribute to improve the graft outcome.

We found that Living donor is the only source for renal transplantation in Iraq

Allograft biopsies form a useful, easy and relatively safe tool for the diagnosis of acute and chronic graft dysfunction.

5. RECOMMENDATIONS

Protocol biopsy is recommended to be adopted in our practice for early detection and treatment of subclinical pathologies to improve graft outcome.

Doing renal allograft biopsy could be the best option for every patient with graft dysfunction before commencing treatment.

The result of allograft biopsies had a great positive impact on the management plan of renal transplant recipients, especially with the use of new biological agents or procedures in management.

Despite the advantage of detecting pathologic events as subclinical acute rejection and relative safety of the procedure; protocol biopsy are still matter of debate, they have not become a standard practice in most transplant center, in addition to lack of clear proof of benefit of early treatment of SAR pathology that revealed by protocol biopsy, despite usefulness of protocol biopsy data on optimal timing are still lacking.

6. LIMITATION OF STUDY

One issue represent major confounder to our study which is the small size sample Furthermore, donor-specific antibody testing and therapeutic drug level were not performed

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