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"The Histopathological Spectrum And Clinicopathological Correlation Of Renal Allograft Failure - What Have We Learnt?"

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ABSTRACT:
Graft dysfunction (GD) in renal allograft transplant is common and biopsy remains the gold standard for diagnosis. The aim of this study was toevaluate the spectrum of histopathological changes in GD and to evaluate the corelation between the causes of graft failurewith the time after transplant, native kidney disease, and types of immunosuppression used.
It was an retrospective, observational study, done in Osmania Medical College and Hospital, Hyderabad, Telangana where the histopathological findings of allograft biopsies in 168 kidney transplant recipients with graft failure were evaluated with respect to demographics, clinical, histological, and immunohistochemical features. Patients with renal vascular causes of GD or death with a functional graft were excluded from study. Rise in serum creatinine, significant proteinuria, or the development of de novo DSA were the indications for USG guided renal biopsy.
168 patients were studied where 73.9% were males with a mean age of 32.2 ± 13 years at the time of transplant. 30.9% patients had chronic glomerulonephritis (CGN) as native kidney disease followed by diabetes (27.3%). 62% received thymoglobulin as induction and 82% received tacrolimus, MMF, prednisolone as maintenance immunosuppression. Mean serum creatinine was 3.8±0.92 mg/dl. Mean interval between biopsy and graft failure was 106.5 ± 104.6 days. 34% of the biopsies were done between 1st week to 6 months post-transplant.
Majority of the causes of GD was rejection (antibody mediated rejection AMR-26.7%, acute cellular rejection ACR-12.5%, chronic allograft nephropathy 6.2%, ACR and AMR in 12.3%) followed by nonrejection causes 36.8% (acute tubular injury 43.4%, cyclosporine nephrotoxicity 19.2%, infections 8.8%, thrombotic microangiopathy 14%, de novo glomerulonephritis or recurrent renal disease) and others. Corelation study shows patients with CGN as native kidney disease have significantly increased risk of developing AMR and recurrence compared to others. There was a significant trend for GD due to acute rejection in the early post-transplant period, while in the late post-transplant period, transplant glomerulopathy was the most common cause of GD. There was significant trend of nonrejection causes of GD in 0-3 years.
In the current era of immunosuppression, non-rejection pathology forms a significant cause of GD post renal allograft transplantation.

KEY WORDS – *Renal transplant, Graft dysfunction, Biopsy, Rejection, ATN*

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I. INTRODUCTION

Renal transplantation has emerged as the treatment of choice for patients with end stage renal disease (ESRD). It provides considerable survival benefit in all age groups with better health related quality of life. It is also cost effective compared to hemodialysis.There has been a 1.6-fold increase in the total number of renal

transplantations in Asian population in the past decade with 994 transplants in 2005 and 1661 transplants in 2015 in Japan.[1]The prevalence of end-stage renal disease requiring transplantation in India is between 151 and 232 per million population.[2]The living kidney transplantation program in India has evolved in the past 45 years and is currently the second largest program in numbers after the USA. In India, about 7500 renal transplants are being done, of which about 90% are from living donors and 10% from deceased donors.[3]

In this era of immunosuppression, there has been significant improvements in early graft survival, however, allograft failure among transplanted kidney recipients is now the fourth leading cause of ESRD in the US.[4] Biopsy remains the gold standard for evaluation of graft dysfunction(GD) despite new developments in the diagnostic modalities for immune injury in renal allograft.[5] The immunological causes can be hyperacute rejection, early acute (<3 months), late acute (3-12 months), and chronic rejection (>12 months).[6] Other causes of GD are acute ischemia reperfusion injury or acute tubular injury/necrosis (ATI/ATN usually <1 month), drug toxicity (<12 months),infections, obstruction/reflux, renal artery stenosis, de novo glomerular diseases, recurrent primary diseases and auto/ alloantibody mediated diseases.[6] Biopsy findings can change the clinical diagnosis in 36% and the therapeutic management in 59% of cases.[6]

Prof. Kim Solez developed a uniform approach to interpret renal transplant pathologies in 1991 as Banff Classification of Allograft pathology.[7] The latest meeting was held in 2019 at Pittsburgh and the updated classification is currently being used. In this study, we have explored the histopathological spectrum of renal allograft failure and corelation between the causes of graft failure with the time after transplant, native kidney disease, and types of immunosuppression used.

II. MATERIAL AND METHODS

Study population and design:A retrospectiverecord-based analysis of 168 ultrasound guided core biopsies of renal transplant cases was performed where renal allograft biopsies from January 2015 to December 2022 were retrieved and reviewed. They were reported using the latest Banff 2019 classification. Patients with incomplete data, renal vascular causes of graft dysfunction, death with a functioning graft were excluded from the study. Routine blood and urine examinations, renal function tests, and therapeutic drug monitoring, were conducted. Biopsy was done as indicated. No protocol biopsies were done. Pyelonephritis and other potential sources of obstruction in the urinary tract were excluded prior to the renal biopsy.

Data Collection:The data on age, gender, cause of ESRD, type of transplant, transplant course, induction and maintenance immunosuppression, time since transplant, clinical evidence of graft dysfunction, creatinine, proteinuria, tacrolimus levels, serological parameters were collected in detail.

Immunosuppression: Patients undergoing renal transplant received induction immunosuppression with either a depleting (anti-thymocyte globulin, ATG) or non-depleting (Basiliximab) agent based on immunological risk factors. The protocol for deceased donor transplants and for high-risk live transplants was to give ATG 3-4 mg/kg in divided doses along with intravenous (IV) methylprednisolone 500 mg on day 0, followed by 250 mg on day 1 and day 2. Basiliximab was used at a dose of 20 mg on day 0 and on day 4.They were maintained on a triple immunosuppressive regimen with a calcineurin inhibitor (CNI, usually tacrolimus at dose of 0.05-0.08 mg/kg/day), anti-proliferative agent (mycophenolate mofetil or mycophenolate sodium MMF/MPS 1g twice daily), and prednisolone (initiated at 40 mg/day, tapered to 10 mg over a period of 2 months), along with valganciclovir for 100 days and cotrimoxazole for 1 year. Tacrolimus levels were measured by fluorescence polarization immunoassay technology; maintaining trough level 7–10 ng/ml in the 1st month and 3–7 ng/ml subsequently; if patient did not receive induction, 8–10 ng/ml for the 1st month and 3–7 ng/ml subsequently.

The above immunosuppressive drugs were given free of cost under the government scheme. The patients were followed up by routine laboratory investigations weekly for the first 1 month, fortnightly for the next 3 months, and monthly thereafter. The investigations were complete urine examination, hemogram, renal function tests, and ultrasound. The trough (C0) level of tacrolimus was measured monthly for the first 6 months, followed by 3 monthly intervals thereafter. Blood cultures, urine cultures, and appropriate investigations were done during infections. Individual adjustment of doses and drug levels were done at physician discretion based on patient's clinical condition including infection, malignancy and rejection. Switching to mTOR inhibitors among failing graft was not a common practice. In the presence of evidence of CNI toxicity on biopsy, CNI trough goal was lowered based on physician discretion.

Kidney allograft Biopsy: The majority of the biopsies were performed on clinical suspicion of GD. The indications for percutaneous biopsy included: (1) increase in the serum creatinine level to >25% above baseline; (2) graft dysfunctions (delayed or slow graft dysfunction), with oliguria or anuria; (3) chronic renal graft dysfunction, i.e., rise of creatinine over a period of months; (4) abnormal urinalysis with either persistent glomerular hematuria and/or proteinuria.Renal biopsy was done using ultrasonography-guided method with a 18-gauge needle (Bard).There were no major complications following the procedure except for the hematuria. About 4.6% of the biopsied patients had gross hematuria which resolved spontaneously after 6–8 hours. Protocol biopsies were not a common practice in the hospital.

Histopathology: Slides of formalin fixed paraffin embedded renal tissue blocks (maximum thickness 3-4 micron) were retrieved and reviewed. Hematoxylin and eosin, Jones methenamine (JMS), periodic acid-schiff (PAS) and trichrome special stains were used for light microscopy. These three special stains (JMS, PAS, and Trichrome) of kit company Roche Ventana were performed using Ventana Benchmark Special stainer and the immunohistochemical stains (IHC) such as C4d and SV40 were performed on Leica Bond III IHC stainer with the retrieval time of 20 minutes for C4d and 40 minutes for SV40. Optimal biopsy was defined as a specimen with at least 10 non-sclerotic glomeruli and 2 arteries. Immunofluorescence analyses (for immunoglobulin A [IgA], IgG, IgM, C1q, C3, and C4d) were done in all biopsies. These were examined by two pathologists in an independent, blinded fashion and were classified as latest modified Banff Classification 2019. The patients were treated accordingly.

Rejection treatment:Treatment of antibody mediated rejection (ABMR), acute cellular rejection (ACR) was done based on standard guidelines.

Statistical analysis:Data entry was done in Microsoft Excel and was analysed with Stata 12 software. Demographic characteristics were summarized with descriptive statistics (mean and standard deviation for continuous variables and frequency and percentages for categorical variables). $P < 0.05$ was considered statistically significant. For time to event data, survival analysis using Kaplan–Meier approach and log-rank test was carried out. Assumption of proportionality of hazard over time was tested before undertaking Cox proportional hazard model.

Patient consent:The patient consent has been taken for participation in the study and for publication of clinical details and images. Patients understand that the names and initials would not be published, and all standard protocols will be followed to conceal their identity.

Ethics statement: The study was cleared by institute's ethics committee. It was done in accordance with Declaration of Helsinki.

III. RESULTS

Study population: A total of 309 patients had allograft failure during the study period. Of these, 168 patients fulfilled our selection criteria and were included in the study.

Recipientcharacteristics (table 1): Out of the 168 patients included in the study, the majority were 124 (73.9%) were males. The mean age at the time of transplant was 32.2±13.7 years. The most common cause of ESRD was glomerulonephritis (30.9%) followed by diabetes (27.3%), chronic kidney disease of undetermined etiology (CKDu) in 17.2%, hypertension (13.09%), cystic kidney diseases (8.3%) and others. The majority were living donor transplants (107, 63.6%). All the live-related transplants had a median haplomatch of 3/6 while spousal had zero matches. The majority received induction immunosuppression agent as ATG (62.4%) followed by Basiliximab (29.7) and others (7.9%). The standard maintenance triple immunosuppression (CNI, MMF and steroids) was given in 88.7%. The mean serum creatinine at the presentation of GD was 3.8±0.92 mg/dl. A total of 24% had developed delayed graft function (DGF). About 17.6% had developed new-onset diabetes mellitus after the transplant. 48.8% of the patients were managed by standard treatment protocols and hemodialysis. 43.4% of the patients haddonor specific antibodies (DSA) within a year prior to the graft failure. The presence of pre-existing DSA prior to the transplant was not checked routinely in all patients. The mean graft survival was 4.9±4.4 years.

Donor characteristics: The mean age of the donors was 42.9 ± 13.05 (range: 16–72) years. Overall, about 48.8% were female and 51.2% were male. Relationship in live donors was mother as donor (n = 42), father (n = 36), sister (n = 7), brother (n = 2), wife (n = 19), father-in-law (n=1) respectively. In deceased donors, 71% were male, while in live-related donors, 69% were female. There were no donations after cardiac death. The mean cold ischemic times were 5.36 ± 2.6 hours.

Biopsy findings (figure 1,2): Non immunological causes of graft failure (62, 36.8%)were the predominant biopsy finding in this study, closely followed by ABMR (45, 26.7%), mixed rejection (21, 12.5%), ACR (14, 8.3%), chronic allograft nephropathy (CAN;13,8.1%). Less common findings were presence of acute tubular injury on chronic allograft nephropathy (ATI on CAN;16,10.1%) andborderline changes of rejection (9, 5.6%). Some patients underwent repeat renal biopsy (n=12). 62 patients revealed non immunological causes of GD in their renal histology. Of them, the majority was acute tubular injury/necrosis (ATI/ATN; 27, 43.4%) followed by cyclosporine toxicity (12, 19.2%), infections (9, 14.4%) and thrombotic microangiopathy (TMA; 5, 8.8%). Hence, the individual contributions of ATI/ATN, cyclosporine toxicity, infections and TMA in the whole spectrum were 15.6%,6.9%,5.2% and 3.1% respectively. 6 cases had recurrence of glomerular diseases and 3 cases had denovo glomerulonephritis.

Common causes of graft failure based on the histological diagnosis: Acute rejection (AR) was the most common cause of graft failure and accounted for 47.5% (26.7% ABMR, 12.5% mixed, 8.3% ACR) of all graft failures. Non immunological causes of GD contributed nextwith majority being ATI/ATN. This study

reported a comparatively lesser incidence (18.2%) of chronic graft failure cases (8.1% CAN, 10.1% ATI on CAN).

Timing of allograft biopsies post-transplant (figure 3): Majority of the biopsies in this study was done between 1st week to 12 weeks of post-transplant period (34.4%) followed by 12 weeks to 12 months (24.2%).

Corelation between histopathological causes of graft failure with cause of ESRD (table 2): The cause of graft failure was further analysed based on three most common causes of ESRD: glomerulonephritis, diabetes and hypertension. AR and recurrence of disease was significantly higher in the glomerulonephritis group compared to others. ATI was increased in the diabetes group. Evidence of mixed rejection was significantly more in patients having hypertension as their native kidney disease.

Timeline of biopsy proven GD (table 3): Among 62 patients having non immunological causes of GD, a significantly greater number of patients (45; 72.6%) presented in early (0-3 years) compared to late (>3 years) post-transplant period (17;27.4%).

Corelation between causes of GD according to time after transplant (figure 4): There was a significant trend for graft failure due to acute rejection in the first post-transplant period ($p<0.01$). Similarly, there was a significant trend of non-immunological causes of GD in the first post-transplant period.

Table 1: Baseline characteristics of the study population

Baseline characteristics	Number (%)
Total number of GD cases	168
Gender	
Male	124 (73.9)
Female	44 (26.1)
Mean age at the time of transplant (years)	32.2±13.7
Causes of ESRD	
Glomerulonephritis	52 (30.9)
Diabetes	46 (27.3)
CKDu	29 (17.2)
Hypertension	22 (13.09)
Cystic kidney diseases	14 (8.3)
Others/CAKUT	5 (2.9)
Mean number of transplants (Range 1-3)	1.01±0.59
Type of transplant	
Living donor transplant	107 (63.6)
Mother	42 (39.2)
Father	36 (33.6)
Wife	19 (17.7)
Sister	7 (6.5)
Brother	2 (1.8)
Father-in-law	1 (1.2)
Cadaver donor transplant	61 (36.4)
Induction Immunosuppression	
Anti thymocyte globulin (ATG)	105 (62.4)
Basiliximab	50 (29.7)
Others	13 (7.9)
Maintenance Immunosuppression	
CNI+MMF+prednisolone	149 (88.7)
Others	19 (11.3)
Mean serum creatinine at the onset of GD (mg/dl)	3.8±0.92
Management	
Requirement of RRT/HD	41 (24.4)
Conservative	45 (26.7)
Both	82 (48.8)
DSA within a year prior to GD	
Present	73 (43.4)
Absent	56 (33.3)
Not tested	29 (17.2)
Mean graft survival (years)	4.9±4.4
Mean interval between biopsy and graft failure (days)	106.5±92.6

GD- graft dysfunction, ESRD- end stage renal disease, CKDu- chronic kidney disease of unknown etiology, CAKUT-congenital anomalies of kidney and urinary tract, CNI-calcineurin inhibitors, RRT-renal replacement therapy, HD-hemodialysis, DSA-donor specific antibodies

Table 2: Corelation between histopathological causes of graft failure with cause of ESRD

	Glomerulonephritis n=52(%)	Diabetes n=46(%)	Hypertension n=22(%)
Antibody mediated rejection	15(28.8) **(p<0.01)**	9(19.5)	4(18.1)

Acute cellular rejection	5(9.6)	3(6.5)	3(13.6)
Mixed rejection	7(13.4)	5(10.8)	6(27.2) **(p<0.05)**
Chronic allograft nephropathy	5(9.6)	3(6.5)	0
Recurrence	6(11.5) **(p<0.01)**	0	0
Acute tubular injury/necrosis	7(13.4)	12(26) **(p<0.05)**	3(13.6)
Cyclosporine toxicity	3(5.7)	5(10.8)	1(4.5)

Table 3: Timeline of biopsy proven graft dysfunction

Renal histology	Immediate (<1 week), n (%)	Early (1 week-12 weeks), n (%)	12 weeks – 12 months, n (%)	1-3 years, n (%)	>3 years, n (%)
ABMR (n=45)	8 (17.7)	7 (15.5)	12 (26.6)	11 (24.4)	7 (15.5)
ACR (n=14)	3 (21.4)	1 (7.1)	4 (28.5)	4 (28.5)	2 (14.2)
CAN (transplant glomerulopathy) (n=13)	0	0	2 (15.3)	4 (30.7)	7 (53.8)
Non immunological causes of GD (n=62)	**13 (20.9)**	**8 (12.9)**	**11 (17.7)**	**13 (20.9)**	**17 (27.4)**
CNI toxicity (n=12)	0	3 (25)	1 (8.4)	2 (16.6)	6 (50)
Recurrence (n=6)	1 (16.6)	2 (33.3)	0	2 (33.3)	1 (16.4)

Figure 1: Spectrum of renal histopathology in graft dysfunction according to revised Banff diagnostic criteria (n=180)

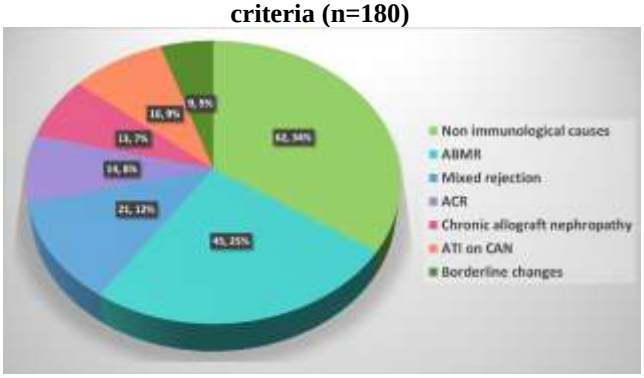


Figure 2: Spectrum of non-immunological causes of graft dysfunction in renal histology (n=62)

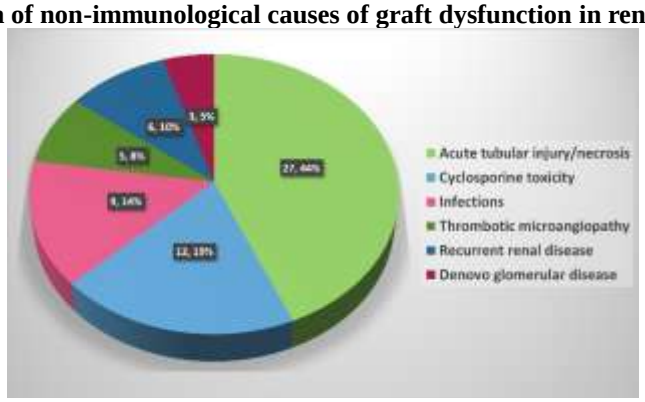


Figure 3: Timing of allograft biopsies post-transplant

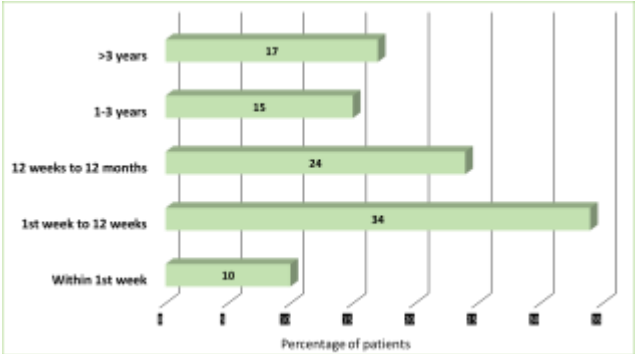
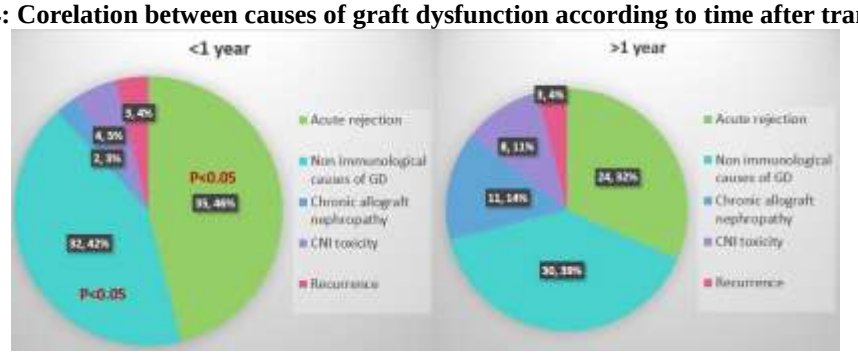


Figure 4: Corelation between causes of graft dysfunction according to time after transplant



IV. DISCUSSION

Incidence of GD: In the new era of immunosuppression, there has been a dramatic decrease in graft failure in the first post-transplant year. ACR rates have decreased to less than 10%.[8]The half-life of a standard criteria deceased donor kidney in the United States has increased by almost 50%, from 10.6 years in 1989 to 15.5 years in 2005.[8]Currently, the ongoing researches target to prevent and manage ABMR. Certain newer therapeutics are considered for ABMR treatment based on their mechanism of action, such as anti-CD20 antibodies (ofatumumab and ocrelizumab), anti-CD22 antibody (epratuzumab), agents targeting B cell activation (atacicept and belimumab), anti-C5 antibody (eculizumab), and others.[9] However, prolonged graft survival is limited by lesser understood mechanisms of transplant glomerulopathy and IFTA. Histopathological evaluation is crucial to differentiate diverse causes of GD. Limited data are available on the etiologies of transplant dysfunction especially in our region, and the purpose of this original article was to contribute to the literature and also help in establishing the local registry.

In this study non rejection causes of GD was the predominant histological finding (36.8%) followed by ABMR (26.7%) and ACR (8.3%). This was in synchrony with a study conducted on 119 biopsies by Philip et al from North India, where the majority (47.1%) were in the non-rejection category.[10] It was followed by TCR (31.9%), AMR (28.6%), IFTA (12.6%), borderline changes (7.6%) and normal (4.2%).[10]This was in contrast to the study by Aryal G et al., who evaluated the histopathology of 98 graft biopsies of which 24.7% were rejection, 14.3% were due to non-rejection causes, 50.1% were normal, 1% was due to IFTA and 9.2% were non-diagnostic.[11]Such discrepant histological findings could be due to differences in type of transplant (cadaver, living related/ un-related), donor and recipient age disparity, race and genetic variability, HLA match, presensitization, immunosuppression availability and adherence, indications and timing of biopsy, variability of renal lesions and pathologist expertise in distinguishing between Banff diagnostic categories. Further in the latter two studies, ACR was the predominant type of rejection compared to ABMR (31.9% vs. 28.6% and 8.16 % vs. 6.12% respectively) unlike our series where ABMR was predominant over ACR (26.7% vs. 8.3%). This was in accordance with the study conducted by Devadass et al from India.[12]

Acute rejection (AR):AR remained the major cause of GD following transplant. Sellares et al showed 35% had AR including ACR, ABMR, and borderline rejection.[13]The advents in newer immunosuppression and better techniques in immunological matching between the donor and recipients have contributed to decrease in AR in the first post-transplant year. Nankivell et al. found that the risk of AR in the 1st year post transplantation was < 15%.[14] In this study, a relatively higher percentage46% (35/76) had developed AR during the 1st year of post-transplant, of which 77% (27/35) were ABMR. (Table 3)

ABMR:The incidence of ABMR has increased in the last few decades with emerging better diagnostic techniques for the detection of antibodies. Heavy immunization, pretransplant therapeutic strategies (blood

transfusion), and re-transplantation led to sensitization and development of anti HLA antibodies.In fact, anti-HLA antibodies were present in about 30% of pretransplant and 25% of unsensitized posttransplant patients.[15] Histologically, active ABMR has been characterized by linear C4d staining in peritubular capillaries, microvascular inflammation, intimal or transmural arteritis, acute thrombotic microangiopathy, and fibrinoid necrosis of arteries. Chronic ABMR had histological features of transplant glomerulopathy (multilayering of glomerular basement membrane), peritubular capillary multilayering, and arterial intimal fibrosis.Late AR can occur in a setting of decreased immunosuppression in the context of infections, drug toxicity, or malignancy. In this study 40% (18/45) patients presented as ABMR after 1st year of transplantation (table 3) and the occurrence had been significantly more in patients with primary glomerulonephritis as underlying cause of ESRD.

ACR: Incidence of ACR has decreased following strict immunosuppression protocols. Torres et al. evaluated 59 allograft biopsies and found cell-mediated rejection in 17 (29%) of cases.[15] It is characterized by interstitial inflammation, tubulitis, and arteritis with various grades. There is an infiltration of T lymphocytes and macrophages in the tubules and interstitium. In this study, 8% of patients had ACR in their renal histology.

Mixed rejection: Wehmeier et al., in their study, reported mixed rejection cases in biopsies from 2.6% in patients without DSA to 14% in patients with DSA.[16] It is more frequent in protocol biopsies where majority of the cases belong to the entity of "subclinical rejection". This study reported evidence of mixed rejection in 12.5% of cases.

Borderline rejection: There is evident that T cell mediated rejection (TCMR) or borderline TCMR can provoke ABMR and compromise long term graft survival. This is still a matter of debate whether it is in the spectrum of TCMR leading to ABMR, or simply two separate parallel findings. Nonetheless, the presence of borderline rejection(5.6%) in this study deserves close monitoring and appropriate management.

IFTA: Nankivell et al found IFTA 2/3 scores in 128 of 1138 patients (11.2%)[14] which was almost comparable as this study. IFTA is more commonly evident in association with mixed rejection and in protocol biopsies. The recent gene expression studies confirmed that even without histological evidence of inflammation IFTA showed a molecular profile of immune-mediated inflammation.[17]

Non rejection causes: In the present study,among the non-rejection causes of graft failure,43.4% cases were contributed by ATI/ATN and this is higher than reported by Mondher et al. in 2012 who found out 39 of 255 (15.29%) patients presented with ATN.[18] This could be attributed to a greater number of patients having diabetic kidney disease as the underlying cause of ESRD as these patients were most prone to microvascular ischemia. Arteriovenous thrombosis, a close differential of ATN had been ruled out by the routine use of color doppler ultrasound. This study was in synchrony to Philip et al study where ATN (25.2%) comprised the largest group of non-rejection category followed by CNI toxicity (16%) and infection (10.9%).[10]

CNI toxicity: CNItoxicity can produce characteristic changes due to epithelial, endothelial and smooth muscle injury. It can be functional due to afferent arteriolar vasoconstriction or it can be structural which can be acute (isometric proximal tubular vacuolisation, intratubular microcalcification, acute tubular injury, thrombotic microangiopathy TMA, vacuolisation in the arterial wall) or chronic (striped/radial fibrosis, peripheral nodular arteriolar hyalinosis, chronic TMA). A study conducted by Sharma et al. found that 88% of the patients had arteriolar hyalinosis and 71% had vacuoles in smooth muscle cells of arterioles in patients with CNI toxicity.[19] In a study by Taheri et al., 8.6% had CNI toxicity.[20] This study had evidence of CNI toxicity in 6.9% of total GD cases which was in contrast tothe study by Zhang et al(10.6%).[21]

Infections: Infections are a major cause of mortality and morbidity among transplant patients and the etiological spectrum varies according to the time period and immune status of the patient. During the initial months post-transplant, bacterial infections deriving from vascular/urinary catheters, surgical sites, urinary tract, respiratory tract predominate followed by opportunistic infections in 1-6 months. Philip et al., identified BKVN (69.2%), tuberculosis (23.1%) and mucormycosis (7.8%) whereas Kumar et al., found that post-transplant TB prevalence was 17%.[10,22] This study revealed urinary tract infections as the predominant source of infection (24%) followed by respiratory tract infections (22%), fungal (18%), CMV (11%), BKV (6%) and others (4%). It also showed incidence of tuberculosis in post-transplant patients was 15%. BK virus nephropathy was characterised by presence of ground glass intranuclear inclusions, nuclear enlargement, cell lysis, denudation of tubular basement membrane, IFTA, tubulitis, and SV40 nuclear positivity. It was treated with reduction in immunosuppression as per protocol.

Recurrence and de novo glomerulonephritis (GN): A study by Jiang et al. found that GN recurrence occurred in 10.5% of transplants and was most common in mesangiocapillary GN (MCGN).[23] Recurrence occurred in 8.7%, 10.8%, 13.1%, and 13.4% of allografts for FSGS, IGAN, MCGN, and MN, respectively at 10 years. Uffing et al. also found that about 32% of the patients developed recurrent FSGS following transplant. Among them, 57% had attained complete to partial response while 43% had no response to rituximab and plasmapheresis.[24] In this study two patients who developed FSGS were treated with rituximab and plasmapheresis but both succumbed to sepsis. It is important to distinguish between the recurrence versus de

novo GN as the occurrence of the latter is rare, usually years post-transplant. Only 3 patients had de novo GN (two MN and one FSGS) in this study.

Clinico histopathological corelation: AR was significantly higher patients where the cause of ESRD was primary GN. This is in accordance with a study where the post-transplant course of 862 renal transplant recipients with primary GN as the cause of their ESRD was studied. This study revealed the incidence rate of acute rejection was 7.2 per 100 person-years compared with 1.4 per 100 person-years for recurrent glomerular disease.[25]Patients with GN often have underlying autoimmune disease or immune dysregulation, and these alterations in the immune system may predispose to acute rejection and impact allograft survival.

Corelation between timing of transplant: This study found that the primary cause of graft failure varies with time after transplantation. It was evident that among the patients with non-immunological causes of GD, the majority presented in early post-transplant period. Therapeutic drug monitoring, strict management of fluid balance in the immediate post-transplant period has been of pivotal importance.

To conclude, timely accurate diagnosis of renal allograft dysfunction is essential for effective management of renal transplant patients. Biopsy remains the gold standard for diagnosis. In the current era of immunosuppression, non-rejection pathology forms a significant cause of renal dysfunction, more so in the early post-transplantation period.

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