Original Article

Histopathological evaluation of renal allograft biopsies: a single center study in Dhaka, Bangladesh

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ABSTRACT

Background: *Renal transplantation is gradually increasing in Bangladesh due to introduction of live transplantation procedure in some of the urology centers in Dhaka. Graft dysfunction followed by graft failure is one of the worst complications of renal transplantation and graft biopsy is the gold standard to evaluate the cause of failure in addition to clinical parameters.*

This study was designed to evaluate the causes of graft dysfunction according to Banff classification and correlation with clinical and laboratory parameters.

Methods: *All the renal graft biopsy samples received at Armed Forces Institute of Pathology during the period from July 2020 to June 2022 were included in the study. Standard histological procedure for renal biopsy including special stains (PAS, Masson Trichrom, Silver) and DIF (IgG, IgA, IgM, C3, C1q, Kappa, Lambda) were applied for all the cases. Immunohistochemistry for C4d and CD3 were also performed for each case. Polyoma virus marker could not be evaluated due to unavailability. BANFF classification was done with the available findings.*

Results: *Total 23 cases were included in this study. All the cases were from live related donors. Mean age of the patients was 34.39 years with male: female ratio 2.28. Time of kidney biopsy from renal transplantation varied from 7 days to 130 months with the average 27.66 months. Graft dysfunction was the indication of the biopsy with average serum creatinine 4.23 mg/dl (range 1.15 to 12.4 mg/dl). Ten (43.48%) of the patients had proteinuria ranging from 1.5 gm to 3 gm/24 hours and 7 (30.43%) patients had haematuria. Among all the cases, 10 (43.48%) came out as Banff category 2 (antibody mediated rejection, ABMR) among them 9 was acute ABMR and one was chronic ABMR. The next common Banff category was Banff 6 (6, 26.09%), which includes IgA nephropathy (2), MPGN (1), CNI toxicity (1), crystal nephropathy (1) and RCN (1). Three (13.04%) were diagnosed as Banff-4 (T cell mediated rejection, TCMR), one (4.34%) was Banff-3 (borderline) and one (4.34%) was Banff-5 (IFTA). Mixed category was observed in 2 cases (Banff-2 + Banff-6). None of the case was diagnosed as Banff-1. Mean age of ABMR was 34.92 years, average duration since transplantation was 20.93 months and mean serum creatinine level was 3.67 mg/dl. Mean age of patients having TCMR was 38.33 years, average duration from transplantation was 59.33 months and mean serum creatinine level 4.71 mg/dl. CNI toxicity was found in a female of 16 years after 10 days of transplantation. One 55 years diabetic male developed graft dysfunction due to crystal nephropathy. One 28-year-old male developed anuria after 7 days of transplantation and diagnosed as post transplant RCN. A 45-year-old male had graft dysfunction after 5 years of transplantation with very high serum creatinine level (12.4 mg/dl) diagnosed as IFTA.*

Conclusion: *Acute ABMR was found to be the prime cause of graft rejection in this study which occured mostly within 2 years of renal transplantation. TCMR occured mostly after 3 years of transplantation. Graft dysfunction due to other than rejection covered 30.43% cases.*

Key words: *renal transplantation, graft dysfunction, BANFF, antibody mediated rejection, T cell mediated rejection.*

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INTRODUCTION

End-stage renal disease (ESRD) patients in Bangladesh is increasing rapidly. No definite country based study is available regarding the exact statistics. According to hospital statistics, approximately 35,000 to 40,000 patients in this country report with ESRD each year. Renal replacement therapy (RRT) is the treatment of choice which includes dialysis and renal transplantation.[1] Renal transplantation is the better choice as it leads to longer survival and enables superior quality of life.[2] Unfortunately, only 25% of ESRD patients in Bangladesh can access RRT and among them, only 2% undergo renal transplantation (RT).[1]

The concept of organ transplantation is relatively new in Bangladesh. The first successful living-related RT was performed at the then Institute of Postgraduate Medicine and Research (IPGMR) in October 1982 in a 29-year-old male. The graft was functioning well but unfortunately the recipient developed pneumonia and died after 4 weeks.[3,4] Until 2003 there was only one center in the country which performed RT. From 2004, other centers started to perform RT in Bangladesh and ten centers in the country were recognized by the government for performing RT. However, only four centers are performing RT regularly. Till 2017, 1791 RTs were performed in Bangladesh.[5]

Renal allograft dysfunction is a major problem in the early post-transplantation period and is recognized as a major cause of graft loss. Improvements in immunosuppression have reduced acute kidney allograft rejection and clinicians are now seeking ways to prolong allograft survival to 20 years or more.[6] Renal allograft biopsy is an important tool to study the status of the RT. It is the accepted gold standard for investigating episodes of graft dysfunction (GF) during post-transplant period. Renal biopsy findings result in altered management decisions in approximately 40% of cases with presumptive diagnosis made on the basis of clinical and laboratory findings.[7,8]

Rejection is the most important but is not the only cause of allograft dysfunction. The other causes of dysfunction are acute ischemic injury, calcineurin inhibitor (CNI) toxicity, infections, chronic obstruction/ reflux, hypertension and recurrent and de novo disease. The Banff classification of allograft pathology, which was developed as a standardized working classification system has contributed to the standardization of definitions for histologic injuries resulting from renal allograft rejections and other injuries. In addition to histological and immunologic parameters, molecular tools are now being used to facilitate the diagnosis.[9,10]

Due to paucity of renal pathology centers even with increasing rate of RT in Bangladesh, most of the GF is dealt clinically without renal biopsy. However, recently a few handful cases are received by the renal pathology centers in Dhaka, Bangladesh. Being one of the few renal pathology centers of Bangladesh, we received only a few renal transplant biopsies at our center in last two years. An attempt has been taken to analyze those cases.

METHODS

All the renal graft biopsy samples received at Armed Forces Institute of Pathology (AFIP), Dhaka, during the period from July 2020 to June 2022 were included in the study. For each case two cores of needle biopsy specimen of renal grafts were received, one in 10% formalin for routine histological procedure and another core of tissue in cool normal saline for direct immunofluorescence (DIF) study. Standard histological procedure for renal biopsy was applied for all the cases including haematoxylene & eosin (H&E) stain and special stains like periodic acid shiff (PAS), masson trichrome, Jones methanamine silver. Ten glomeruli and two arteries in paraffin section specimen is considered as optimal and <10 glomeruli single artery were considered as suboptimal; however all the cases were taken in the study cohort. For direct immunofluroscence (DIF) IgG, IgA, IgM, C3, C1q, Kappa, Lambda were applied for all the cases. Immunohistochemistry (IHC) for C4d and CD3 were also performed following standard antigen retrieval on sections from formalin fixed paraffin embedded tissue. Polyoma virus marker could not be evaluated due to unavailability. Banff classification was done with the available histopathology, DIF and IHC findings. Three histopathologists were involved in the finalization of the cases. The entire received specimen was accompanied by request form of concern nephrologist containing demography, date of transplantation, details clinical information and investigation findings.

RESULTS

Total 23 renal allograft biopsies from live related transplantations were included in the study. Mean age of the recipients is 34.39 years ranging from 16 to 55 years and there was male predominance (Table I). Duration of biopsy from renal transplantation varied from 7 days to 130 months with the average 27.66 months. Graft dysfunction was the indication of the biopsy with average serum creatinine 4.23 mg/dl (range 1.15 to 12.4 mg/dl). Ten (43.48%) of the patients had proteinuria ranging from 1.5 gm to 3 gm/24 hours and 7 (30.43%) patients had haematuria (Table I).

Table I. Demographic and clinical/laboratory characteristics of cases (N = 23)

Parameter		Characteristics
Age of the recipient	Age range of recipient	16-55 yrs
	Mean age	34.39 + 10.58
Gender	Male	16 (69.57%)
	Female	7 (30.43%)
	Male:Female	2.28
Biopsy after transplantation (months)	Mean	27.67 months
	< 1 month	5 (21.74%)
	>1month-6 months	2 (8.69%)
	>6 months-12 months	4 (17.39%)
	>12 months-60 months	11 (47.83%)
	>60 months	1 (4.35%)
Serum creatinine during biopsy	Mean	4.23 mg/dl
	< 1.5 mg/dl	3 (13.04%)
	1.5-5.0 mg/dl	11 (47.83%)
	>5.0 mg/dl	9 (39.13%)
RBC in urine	Present	7 (30.43%)
Proteinuria	Present	10 (43.48%)
UTP >3 gm/24 hrs		2 (8.69%)

Table II shows different Banff categories of GF in this study. According to adequacy criteria, 13 (56.52%) were optimal and 10 (43.48%) were suboptimal. Among all the cases 10 (43.48%) came out as BANFF category 2 (ABMR) among them 9 were acute ABMR and one was chronic ABMR. The next common BANFF category was BANFF 6 (6, 26.09%), which included IgA nephropathy (2), MPGN (1), CNI toxicity (1), crystal nephropathy (1) and RCN (1). Three (13.04%) were diagnosed as BANFF category 4 (TCMR), one (4.34%) was BANFF category III (borderline) and one (4.34%) was BANFF category 5 (IFTA). None of the case

Table II. Characteristics of different Banff Categories (N=23)

Banff diagnostic category (N=23)		No (%)	Mean age (Yrs)	Duration of transplant (Month)	Mean creatinine
ABMR Banff Category-2 (10)	Acute ABMR	9 (39.13)	37.33	19.89	3.09
	Chronic ABMR	1 (4.34)	30	36	5.6
Borderline Banff Category-3 (1)	1 (4.34)	24	2	1.5	
TCMR Banff Category-4 (3)	3 (13.04)	38.33	59.33	4.71	
IFTA Banff Category-5 (1)	1 (4.34)	45	60	12.4	
Others Banff Category-6 (6)	IgA nephropathy	2 (8.69)	30.5	54	5.65
	MPGN	1 (4.34)	28	36	2.8
	CNI toxicity	1 (4.34)	16	0.5	2.5
	Post ischemic RCN	1 (4.34)	28	0.5	6.0
	Crystal nephropathy	1 (4.34)	55	0.2	5.4
Mixed (2)	IgA nephropathy + Rejection	1 (4.34)	26	36	1.8
	RCN + Rejection	1 (4.34)	27	0.2	8.72

diagnosed as BANFF category 1. Mean age of patients having ABMR was 34.92 years, average duration from transplantation 20.93 months and mean serum creatinine level was 3.67 mg/dl. Mean age of patients having TCMR was 38.33 years, average duration from transplantation 59.33 months and mean serum creatinine level 4.71 mg/dl. CNI toxicity was found in a female of 16 yeara after 10 days of transplantation. One 55-year-old diabetic male developed graft dysfunction due to crystal nephropathy. One 28-year-old male developed anuria after 7 days of transplantation and diagnosed as post transplant ischemic RCN. A 45-year-old male had graft dysfunction after 5 years of transplantation with very high serum creatinine level (12.4 mg/dl) diagnosed as IFTA. Two of the cases had double pathology, one had associated IgA nephropathy with ABMR and one had RCN with ABMR. Figure 1 and 2 depicted a few snaps of renal dysfunction cases.

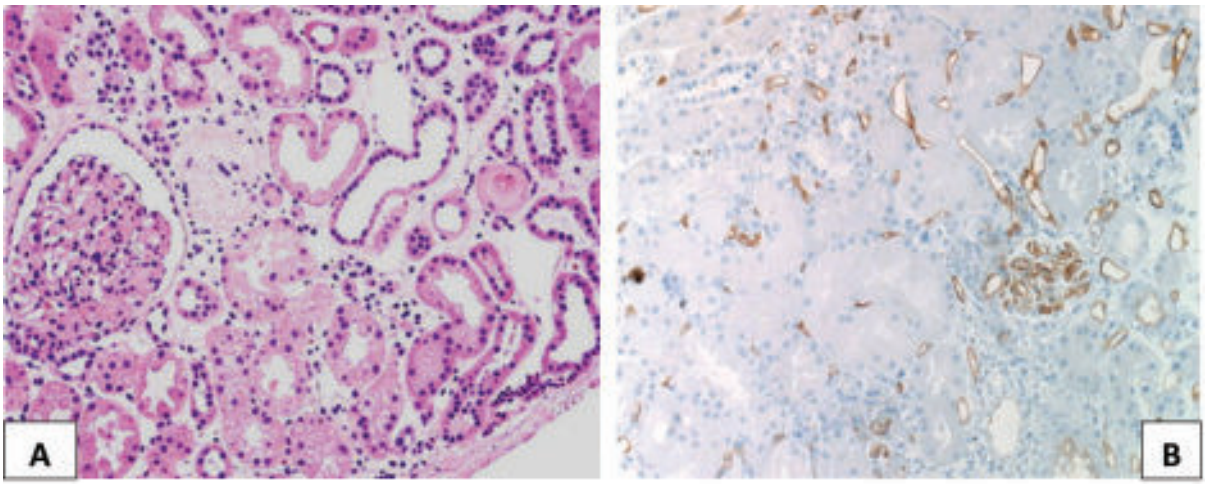

Figure 1. Active antibody mediated rejection. A) H&E stain, B) Immunohistochemistry for C4d.

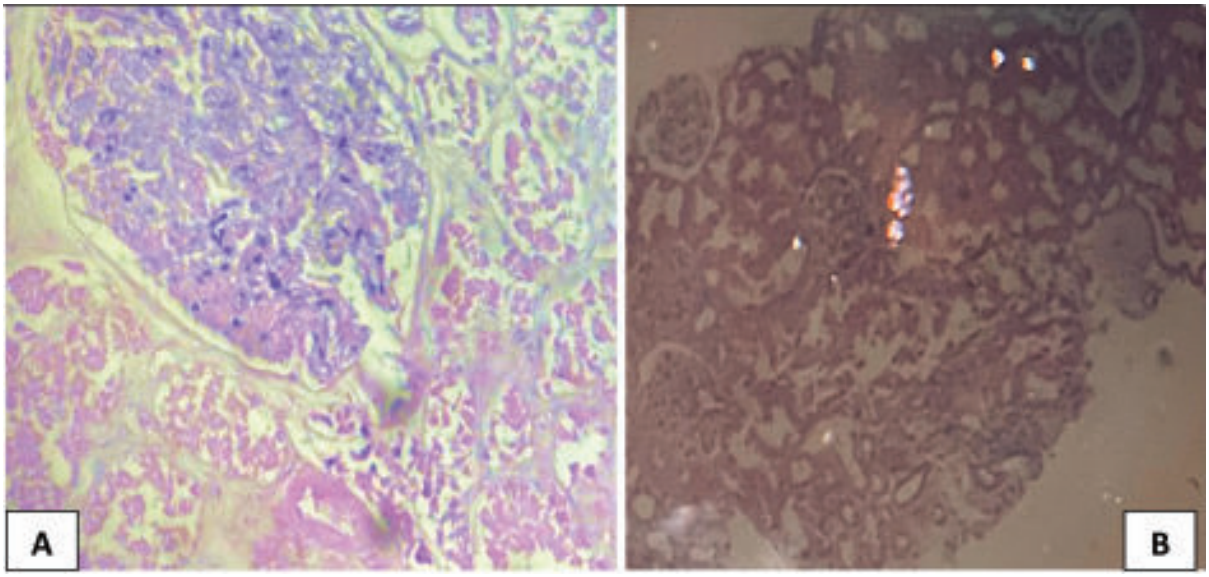

Figure 2. BANFF category 6. A) Cortical necrosis, B) Crystal nephropathy.

DISCUSSION

Renal transplant is a time tested management of ESRD worldwide. Dialysis provides a temporary relief to the patient but for long term management, the renal transplant has been adopted as a favored approach in the past decades.[11] Renal allograft biopsy is the most sensitive diagnostic tool for determining the cause of graft dysfunction.[12] In last few years RT is being performed routinely in Bangladesh by some dedicated RT centers. As such requirement of renal allograft biopsy has been felt by the renal pathologists of the country. In this study we have included the allograft biopsy cases received in our center in two years duration.

The mean age of the transplant recipients and male female ratio are quite closer to study carried out in Pakistan[13], Nepal[12], Egypt[14] and UK[15]. All the transplants were from live related donors. Though according to the human organ transplantation act in Bangladesh, there is no bar for cadaver transplantation but till January 2023, no cadaveric transplantation of kidney is performed.[16,17]

The indication of renal transplant biopsy in all the cases is graft failure, identified by raising serum creatinine level or not decreasing the serum creatinine level, one week after transplantation. The mean serum creatinine level was 4.27 + 2.95 mg/dl, ranged from 1.15 to 12.4 mg/dl. Muhammad MEE et al got serum creatinine 3.74 + 1.73 mg/dl in Egypt.[14] Proteinuria is reported to be found in about 40% of renal transplant recipients.[18] In our study with the renal dysfunction, 30.43% recipients had haematuria and 43.48% had proteinuria. In a study Kim S, et al got haematuria in 245 out of 1300 renal transplant cases (18.84%).[19]

In this study the predominant cause of GF was due to acute ABMR which covers in 37.33% cases and only one (4.34%) was chronic ABMR. TCMR was found in 13.43% cases. Borderline rejection was also found only in one case (4.34%). Bashir S, et al in their study in Pakistan[13] found acute ABMR in 21% cases, while Devadass CW, et al found ABMR in 17.2% cases in India.[20] In this study proportion of ABMR is high in comparison to other studies in this region, which may be explained by small cohort and biopsy only in advance GF cases.

Banff category 6 was the second (26.08%) common cause after ABMR, which included denovo IgA nephropathy (2), MPGN (1), CNI toxicity (1). One 55-year-old male developed crystal nephropathy after transplantation. There were two post ischemic RCN among those one was associated with ABMR. Another patient had dual pathology composed of ABMR and IgA nephropathy. Banff category 5 (IFTA) was seen in one recipient. Munib S, et al in Pakistan got BANFF category 6 in 36.5% cases and BANFF category 5 in 34.62% cases.

In this study acute ABMR was detected within 2 years of transplantation while chronic ABMR was found around 3 years of transplantation. TCMR and IFTA were detected around 5 years of transplantation. Post ischemic RCN, CNI toxicity and crystal nephropathy were reported within one month of transplantation. While Chand S, et al got acute ABMR at around 5 years of transplantation and chronic ABMR at around 13 years of transplantation. They got GF within one month mostly due to surgical causes and primary non-function. IFTA was reported in their study after 15 years of transplantation.[22] The study by Aryal G, et al got mostly normal findings within one week of transplantation along with some acute ischemic injury cases. They got rejection cases both ABMR and TCMR within one year of transplantation and a few CNI toxicity at around one year of transplantation.[12] So there were wide variations of duration of GF due to different etiology in different studies including our study. In our study higher level of serum creatinine was found in post ischemic RCN and IFTA. Devadass, et al got higher level of serum creatinine in renal vein thrombosis and TMA.

Conclusion

Acute ABMR was found to be the prime cause of graft rejection in this study which occured mostly with in 2 years of renal transplantation. While TCMR occured mostly after 3 years of transplantation. Graft dysfunction due to other than rejection covered 30.43% cases. In this study there were wide variation of duration of graft dysfunction after transplantation unlike other studies. The study is limited by small cohort and lack of polyoma viral marker (SV40).

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