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Renal allograft biopsies in elderly renal transplant patients

[1]Kamal V. Kanodia, M.D. (Path & Bact.), P.D.C.C.(Renal and Transplant Path),Professor, Dept. of Pathology, Lab Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

[2]Aruna V Vanikar , M.D. (Path & Bact.), Professor and Head, Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

[3]Lovelesh K Nigam , M.D. (Path), Assistant Prof., Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

[4]R. D. Patel , M.D (Path & Bact.),Professor, Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

[5]Kamlesh S. Suthar M.D. (Path & Bact.), Associate Prof., Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

Corresponding Author: Kamal V. Kanodia, M.D. (Path & Bact.), P.D.C.C.(Renal and Transplant Path),Professor, Dept. of Pathology, Lab Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre and Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, INDIA

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Abstract

Introduction: End-stage renal disease (ESRD) patients are increasing in elderly population worldwide and renal transplantation (RT) is the preferred treatment.

Material and Methods We studied 42 renal allograft biopsies (RAB) performed for graft dysfunction (GD) in elderly patients aged ≥ 60 years to study pattern and timeline of various injuries. Out of the 42 RABs performed, 14 (33.3%) belonged to group-I living donor renal transplantation (LDRT) and 28(66.7%) belonged to group-II, deceased donor renal transplantation (DDRT). Male recipients were more than females (M: F: 34:08). Overall mean age of study population was 63.23 ± 2.22 years and mean SCr was

3.29± 1.76 mg/dl. RAB were performed at 50.65 ± 46.57 months and 17.09 ± 29.84 months posttransplant in LDRT and DDRT recipients respectively.

Results: In LDRT patients, acute TCMR was most common lesion with early graft dysfunction, and chronic ABMR in late graft dysfunction. In DDRT, ATN was the most common lesion with early graft dysfunction and chronic ABMR, chronic CNIT and IF/TA were common lesions with late graft dysfunction. In LDRT recipients, 1- and 5-year patient survival was 100% and 91.7%, death-censored graft survival was 100% and 92.3% respectively. In DDRT recipients, 1 and 5-year patient survival was 78.6% and 66.3%, death-censored graft survival was 100% and 92.9% respectively.

Conclusions: Renal biopsy remains the gold standard for diagnosis, management and prognosis of allograft dysfunction. In elderly RT patients, biopsy monitoring and tailor-made immunosuppression should be encouraged.

Key words: Elderly patients, renal biopsy, living donor renal transplantation (LDRT), deceased donor renal transplantation (DDRT)

Introduction

End-stage renal disease (ESRD) patients are increasing in elderly population worldwide.[1] Renal transplantation (RT) is the preferred treatment compared to dialysis as it offers greater longevity, better quality of life and is cost effective.[2]

There is no absolute upper age limit to exclude an individual for RT. Overall health and quality of life would be more appropriate to decide the benefits of transplantation in a given elderly patient.[3] According to the guideline of the Canadian society of transplantation, advanced age per se is not a contraindication for RT.[4]

Age related co-morbidity is however an important limiting factor and active infection or recent malignancy are absolute contraindications.[3,5] So assessment of recipients for cardiovascular disease, malignancy and other comorbidities like mental illness and dementia should be done before transplantation.

Renal dysfunction secondary to immunological and non-immunological injuries including drug toxicity can occur in post-transplant patients of any age irrespective of duration of post-transplant period. Renal allograft biopsy (RAB) is the gold standard for diagnosis of allograft dysfunction.

We studied the spectrum of injuries with respect to timeline on indicated RAB in elderly RT patients with graft dysfunction. We also compared the outcome of living donor renal transplantation (LDRT) and deceased donor renal transplantation (DDRT).

Material and Methods

This was an Institutional Review Board approved retrospective study of indicated diagnostic RAB for graft dysfunction performed from January, 2011 to December, 2018. Elderly patients aged 60 years or above and who had undergone LDRT / DDRT were included in the study.

Patients were divided in two groups: Group-I: Elderly patients who underwent LDRT (N=14); Group-II: Patients who underwent DDRT (N=28). All patients received standard triple immunosuppression (IS) comprising of Prednisolone, Calcineurin inhibitors (CNI) and/or Mycophenolate mofetil (MMF) or Azathioprine.

For light microscopic assessment 3 μm thick paraffin embedded sections were stained with Hematoxylin and Eosin, Gomori's trichrome, periodic acid Schiff and Jone's silver methaneamine stains. Immunohistochemistry for C4d stain was performed as

per the manufacturer's protocol using "Novolink™ Polymer Detection System" (Leica Biosystems, Germany) with rabbit anti-human C4d monoclonal antibody (clone SP91, Spring Bioscience, USA) and Novolink™ Polymer Anti- rabbit Poly-HRP-IgG.

All the biopsies were assigned categories as per Revised Banff'17 Schema for reporting RAB.[6] A panel of 5 pathologists independently reviewed the biopsies and consensus diagnosis generated was finally reported. Graft function was measured in terms of serum creatinine (SCr) (mg/dL).

Statistical analysis: Data was analyzed using SPSS V20 .Continuous data was expressed as mean ±1 S.D. They were parametric and non-parametric. Independent t-test and Mann Whitney test were used to calculate p-value. Non-Continuous data was expressed in frequency and in percentages. Chi Square test and Fisher Exact test were used for finding significant value. A p-value < 0.05 was considered as statistically significant.

Results

Forty two RABs were performed. Out of the 42 RABs, 14 (33.3%) belonged to group-I (LDRT) and 28(66.7%) belonged to group-II (DDRT). Male recipients were more than females (M:F: 34:08). The M;F ratio was 13:01 in group-I and 21:07 in group- II.

Overall mean age of study population was 63.23 ± 2.22 years. Mean age of patients in group I and group II was 62.93±1.77 years and 63.38±2.43 years respectively.

The overall mean SCr was 3.29± 1.76 mg/dl and the mean SCr in group I and group II was 2.47±1.05mg/dl and 3.69±1.91 mg/dl respectively.

The predominant native kidney disease was diabetic nephropathy (DN) in 20 (47.6%) followed by hypertensive nephropathy (HTN) in 3(14.28%) patients. Autosomal dominant polycystic kidney disease (ADPKD) and chronic tubulointerstitial nephritis (CTIN) were seen in 2(4.7%) cases each.

Mean time of post-transplant biopsy of all patients was 28.28±39.12 months. Mean post-transplant biopsy time in group-I and group-II was 50.65 ± 46.57 months and 17.09±29.84 months respectively. The overall mean age of donor was 53.68 ± 21 years and mean age of donor in group I and group II was 52.68±21 years and 54.58±24.58 years respectively. [Table 1]

In group-I, 3(21.4%) biopsies were performed in <1 month post-transplant period. Out of these, 2(14.2%) biopsies revealed acute T-cell mediated rejection (TCMR) and 1(7.14%) revealed active antibody-mediated rejection (ABMR) along with borderline TCMR. None of the patients were biopsied between 1-12 months. Eleven (78.6%) biopsies were performed 12 months post-transplant. Out of these chronic ABMR was seen in 4(28.6%) biopsies. Two (14.3%) biopsies revealed chronic calcineurin inhibitors toxicity (CNIT), 2 (14.3%) revealed chronic ABMR with chronic CNIT, and 2 (14.3%) revealed interstitial fibrosis with tubular atrophy (IF/TA) of unexplained origin. Acute pyelonephritis was observed in 1(7.14%) biopsy.

In group-II, 18(64.3%) biopsies were performed in <1 month post-transplant, of which acute tubular necrosis (ATN) was seen in 8(28.6%) and active ABMR was seen in 4(14.3%) biopsies. Acute TCMR was seen in 3(10.7%) biopsies and active ABMR+ borderline TCMR was seen in 3(10.7%) biopsies. Within 1-12 months post-transplant, 2(7.14%) biopsies were performed. Active ABMR and acute CNIT was reported in 1(3.65%) biopsy each. After 12 months, 8(28.6%) biopsies were performed. Of these, chronic ABMR, chronic CNIT, IF/TA, chronic ABMR+chronic

CNIT were reported in 2(7.14 %) biopsies each. [Table 2]

In group-I, one year and five year patient survival was 100% and 91.7% respectively. Death-censored graft survival at one year and five year was 100% and 92.3% respectively. Mean SCr at one and five years was 1.25±0.44 mg/dL and 1.64±0.44 mg/dL respectively.

In group-II, one year and five year patient survival was 78.6% and 66.3% and death-censored graft survival was 100% and 92.9% respectively. Mean SCr at one and five years was 2.26±1.54 mg/dL and 1.89±0.52 mg/dL respectively.

Discussion

Elderly ESRD patients are treated with RT in absence of contra-indications. DN and HTN were predominant primary causes of ESRD leading to RT.[2] RT decreases mortality in these patients when compared to patients on dialysis. [2]

In present study, the mean time of post-transplant biopsy was more in group-I than in group-II, which was statistically significant. The number of allograft biopsies performed was more in group-II compared to group-I. In <1 month post-transplant period 64.3% biopsies were performed in group-II and only 21.4% in group-I, suggesting that early graft dysfunction was more in group-II.

Prevalence of biopsy proven acute rejection was 21.4% in group-I and 35.7% in group-II in our study. Other authors have also reported the prevalence of acute rejection of 12.6% to 34% in elderly RT patients.[7,8,9] Our study is one of the few studies that have compared the biopsy findings in elderly patients who have undergone LDRT and DDRT. [8] The most common biopsy finding at <1 month post-transplant was acute TCMR in LDRT and ATN in DDRT group.

Acute rejection is less common in older patients because of a less active immune system. [7,10,11] Elderly patients have natural immunosenescence so they require less immunosuppressant dose which is associated with decreased cardiovascular risk and infection in addition to improved recipient and graft survival.[12,13] However these patients are at an increased risk of infectious death mainly in the first year after transplantation when immunosuppression is the highest compared to younger recipients. [2,14,15] Transplantation in elderly patients have 41% to 76% lower mortality compared to waitlist dialysis patients.[2,16,17] High donor age and increased time on dialysis before transplantation have been shown to be risk factors for poor outcome. [18] Acute rejection during the first 3 months after transplantation is a major risk factor for premature death in elderly RT patients.[15]

Patient survival in DDRT was 66% to 76% at 5 years in different studies. [2,8,9] In the present study 5 year patient survival was 91.7% in LDRT, and 66.3% in DDRT group. Patient loss was mainly due to infection and cardio-vascular disease.

Death censored graft survival at 1 and 5 years was 100% and 92.3% in LDRT and 100% and 92.9% in DDRT. In other studies death-censored graft survival in LDRT was 95.8% and 97.3% at 1 year and 92.5% in 5 years. [2,8] Whereas in DDRT death-censored graft survival was of 90% and 95.8% at 1 year and 85.1% at 5 years.[2,8]

Conclusion

In LDRT patients, acute TCMR was the most common lesion with early graft dysfunction, and chronic ABMR in late graft dysfunction. In DDRT, ATN was the most common lesion with early graft dysfunction and chronic ABMR, chronic CNIT and IF/TA were common lesions with late graft dysfunction. The

incidence of acute rejection is lower in this group of patients. Patient and graft survival are acceptable in both groups. The graft as well as patient survival is comparable in RT patients irrespective of type of RT (LDRT or DDRT).

RT is a viable option in elderly and RAB remains the gold standard for diagnosis, management and prognosis of allograft dysfunction. Biopsy monitoring and tailor-made immunosuppression should be encouraged in elderly RT patients.

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Legend Tables

Table 1: Demography of two groups (n=42)

Demography (n ± SD)	Total	Group-I (LDRT)	Group-II (DDRT)	P - VALUE
Recipients				
Number of allograft biopsies	42 (100%)	14 (33.3%)	28(66.7%)	-
Mean Age (years)	63.23±2.22	62.93±1.77	63.38±2.43	0.54
Sex: Male: Female	34: 08	13:01	21:07	0.23
S. Creatinine (mg/dL)	3.29±1.76	2.47±1.05	3.69±1.91	0.01
Mean time of biopsy after transplantation (months)	28.28±39.12	50.65 ± 46.57	17.09 ± 29.84	<0.01
Primary Renal Diseases				
Diabetic nephropathy	20	6	14	0.66
Hypertensive nephropathy	11	3	8	0.72
CKDu	7	4	3	0.20
CTIN	2	1	1	1.0
ADPKD	2	0	2	0.54
Donor Age (years)	53.68 ± 21	52± 12.62	54.58 ± 24.59	0.73

Abbreviation: LDRT : living donor renal transplantation, DDRT: deceased donor renal transplantation, CKDu : Chronic kidney disease of unknown origin , CTIN : Chronic tubulointerstitial nephritis ADPKD : autosomal dominant polycystic kidney disease

Table 2: Histological findings corresponding to the timing of biopsies in Living donor transplantation (LDRT) and Deceased donor transplantation (DDRT)

Histological findings	<1 month (Post RT)	1-12 months (Post RT)	>12 months (Post RT)
Group-I (LDRT)			
Acute TCMR	2(14.2%)	0	0
Active ABMR+ Borderline TCMR	1 (7.14%)	0	0
Chronic ABMR	0	0	4(28.6%)
Chronic CNIT	0	0	2(14.3%)
Chronic ABMR+Chronic CNIT	0	0	2(14.3%)
IFTA	0	0	2(14.3%)
Acute Pyelonephritis	0	0	1(7.14%)
Group-II (DDRT)			
ATN	8(28.6%)	0	0
Active ABMR	4(14.3%)	1(3.65%)	0
Acute TCMR	3(10.7%)	0	0
ABMR+Borderline TCMR	3(10.7%)	0	0
Chronic ABMR	0	0	2(7.14%)
Chronic ABMR+Chronic CNIT	0	0	2(7.14%)
Chronic CNIT	0	0	2(7.14%)
Acute CNIT	0	1(3.65%)	0
IFTA	0	0	2(7.14%)

Abbreviations: RT: Renal Transplant, TCMR: T-cell mediated rejection, ABMR: active antibody-mediated rejection, CNIT: calcineurin inhibitor toxicity, IFTA: interstitial fibrosis with tubular atrophy, ATN: acute tubular necrosis