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Study of the Spectrum of Pathological Findings in Renal Transplant Recipients with an Asymptomatic Slow Rise in Serum Creatinine at a Tertiary Care Centre in North India

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Chronic allograft dysfunction, characterized by a progressive increase in serum creatinine levels after kidney transplantation, poses a significant challenge in renal transplant recipients.
Aim: This study aimed to assess the spectrum of pathological findings in renal transplant recipients with an asymptomatic slow rise in serum creatinine.
Methodology: A hospital-based cross-sectional study was conducted, including patients who underwent kidney transplantation and exhibited a creeping rise in creatinine within 3 months to one year. Renal biopsies were performed, and the samples were analysed using various techniques.
Results: Among 30 patients included in the study, a high prevalence of acute tubular

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necrosis20%(n=6), active antibody-mediated rejection20%(n=6),chronic active antibody-mediated rejection20%(n=6), chronic allograft injury10%(n=3), chronic T cell-mediated rejection10%(n=3), acute cellular rejection10%(n=3), membranous nephropathy(n=1), C3 glomerulonephritis(n=1), and cortical necrosis(n=1) was observed. The timing of biopsy post-transplantation and donor HLA mismatch were also evaluated.

Conclusion: These findings emphasize the importance of early detection and proper management of pathological conditions contributing to chronic allograft dysfunction to improve long-term outcomes following kidney transplantation.

Keywords: Chronic allograft dysfunction; renal transplant; serum creatinine; graft failure.

1. BACKGROUND

A progressive increase in the serum creatinine level over time occurs in some patients following kidney transplantation. Creeping creatinine after kidney transplantation is a prominent characteristic of allograft dysfunction. After using calcineurin inhibitors, there has been a marked improvement in graft and patient survival since mid-1980. The purpose of this review is to outline the current assessment of renal dysfunction, define its causes, and the spectrum of pathological findings in renal transplant recipients to ameliorate chronic allograft dysfunction. Chronic allograft nephropathy has several causes: ischemia-reperfusion injury, ineffectively or untreated clinical and subclinical rejection, and superimposed calcineurin inhibitor nephrotoxicity, exacerbating pre-existing donor disease.

The creeping rise of creatinine levels post-transplant is a critical concern in the realm of organ transplantation, casting a shadow over the otherwise life-transforming procedure.

The urgency of this issue lies in its ability to foreshadow a cascade of complications, ranging from acute kidney injury to chronic graft dysfunction. The creeping elevation of creatinine levels is akin to a silent alarm, signaling an underlying imbalance that demands immediate attention. The gravity of the situation is amplified by the fact that post-transplant, patients and clinicians alike strive for a delicate equilibrium to ensure graft survival and overall well-being.

This phenomenon not only poses a direct threat to the transplanted organ but also has broader implications for the quality of life of the transplant recipient. As creatinine levels stealthily ascend, the specter of complications looms large, potentially unraveling the promise of a renewed lease on life.

In essence, the creeping creatinine post-transplant serves as a harbinger of challenges that, if left unaddressed, can erode the transformative impact of organ transplantation. This study endeavors to delve into the depths of this issue, shedding light on the intricacies that demand our attention, in the pursuit of refining post-transplant care and ensuring the enduring success of this life-saving medical intervention.

2. INTRODUCTION

Creeping creatinine, an unexplained elevation in serum creatinine levels persisting for at least three months but not exceeding 12 months before a biopsy, has been identified as a potential indicator of progressive renal allograft dysfunction [1]. Specific histopathological markers, such as striped cortical fibrosis, new-onset arteriolar hyalinosis, and tubular microcalcification, aid in differentiating calcineurin-inhibitor nephrotoxicity from other causes of graft dysfunction [2,3]. Accurate diagnosis and timely intervention are essential for improving long-term outcomes following kidney transplantation [4].

2.1 Aim and Objective

Assessment of spectrum of all pathological findings in a renal transplant recipient with an asymptomatic slow rise in serum creatinine.

3. METHODOLOGY

The study was conducted after approval of the Ethical Committee. All patients who received a deceased/living donor kidney transplant after 3 months and had a slow creeping rise in creatinine were eligible for inclusion. Patients were informed about the study before kidney biopsy and were done as standard care of practice for the treatment of the patient. All those who meet the inclusion criteria and give consent to participate were enrolled.

3.1 Inclusion Criteria

Renal transplant recipients with a slow rise in serum creatinine equal to or >30% over baseline within three months to one year.

3.2 Exclusion Criteria

Renal transplant recipients

- With an acute rise in serum creatinine of more than 25% from baseline within 7 days.
- with acute kidney injury
- With apparent acute calcineurin inhibitor toxicity on clinical and other parameters.
- with apparent infection
- with no adherence to drugs

3.3 Study Design

Hospital-based cross-sectional study.

3.4 Study Period

March 2022 to March 2023.

3.5 Procedure

All post-transplant biopsies were done under ultrasound guidance using a spring-loaded 18-gauge biopsy gun and local anaesthesia with 2% lignocaine under aseptic conditions. Two cores were obtained. The standard procedure of renal biopsy was followed. Biopsies were analysed by light microscopy and immunofluorescence by experienced pathologists and scored using Banff's schema. C4d staining was also performed and if required electron microscopy study. CNI (tacrolimus/cyclosporine) drug levels were monitored simultaneously.

3.6 Statistical Analysis

The SPSS statistical package was used for data analysis. Student's *t*-test and Fisher exact test were used to compare continuous and categorical data, respectively. A p-value of less than 0.05 was considered statistically significant. Multiple linear regression analysis was used to measure the effect of donor age, HLA mismatches, cyclosporine, and mycophenolate mofetil (MMF) use.

4. RESULTS

In this study, we analysed 30 renal transplant recipients. The average age of the participants was 31.9 years with a predominance of males (86%) (Table 1,2). We conducted 29 biopsies in first-time transplant recipients and one in a second-time recipient. Donor-recipient HLA mismatch was categorized as 0-I (2 cases), II-IV (21 cases), and V-VI (7 cases). Biopsies were performed within 3 months, between 3 and 6 months, and beyond 6 months post-transplantation. Patients exhibited an asymptomatic rise in serum creatinine from an

Table 1. Demographic and clinical characteristics of the study population

Characteristics	Numbers (median)
Age	31.9
M: F	26:04
first transplant	29
second transplant	1
HLAmismatchh	
0-I	02
II-IV	21
V-VI	7
time of biopsy after transplantation(months)	
0 to 3 months	4
3 to 6 months	7
>6 months	19
baseline creatinine mg/dl(avg)	1.2
creatinine at biopsy mg/dl(avg)	2.09
baseline immunosuppression	
cyclosporine based	2
TAC based	28
sirolimus based	0

TAC – Tacrolimus

Table 2. Numbers of patients according to age group

Recipients age	Numbers
11 to 20	2
21 to 30	16
31 to 40	8
41 to 50	4

Table 3. Pathological spectrum of allograft biopsy

Pathological spectrum	Numbers
Active antibody-mediated rejection	6
Acute cellular rejection	3
Acute tubular necrosis	6
Chronic allograft injury	3
Chronic aABMR	6
Chronic TCMR	3
Cortical necrosis	1
Membranous nephropathy	1
C3GN	1

a ABMR - Active antibody-mediated rejection ,TCMR- T-cell-mediated rejection, C3GN- C3 glomerulonephritis

average nadir creatinine of 1.2 to an average of 2.09. The majority of patients (28 out of 30) received tacrolimus-based triple immunosuppression, while two patients were on a cyclosporine-based regimen (Table 3). The study aimed to investigate the causes of graft dysfunction considering these factors.

We found a high prevalence of acute tubular necrosis 20%(n=6), the majority of which were presented within 6 months of transplantation found to be significant($p<0.05$), active antibody-mediated rejection 20%(n=6),chronic active antibody-mediated rejection 20%(n=6), chronic allograft injury (CAI) 10%(n=3),chronic T cell-mediated rejection 10%(n=3),acute cellular rejection (n=3)10%, membranous nephropathy (n=1)and C3(n=1) glomerulonephritis 3% and cortical necrosis 3%(n=1).

5. DISCUSSION

Our analysis of 30 renal transplant recipients revealed significant findings regarding the prevalence and distribution of different histological patterns responsible for graft dysfunction, providing valuable insights for the management and understanding of post-transplant complications.

The high prevalence of acute tubular necrosis (ATN), accounting for 20% of cases, was a noteworthy finding in our study. ATN is a common complication following renal transplantation, often related to hypoperfusion, cold ischemia times, harvesting, anastomosis, surgical approach, and the administration of cyclosporine following transplantation [5-8]. The majority of ATN cases manifested within 6 months of transplantation, necessitating close monitoring during this period, as ATN can persist for up to two to three months, especially when cyclosporine is used [9,10]. The administration of calcium channel blockers has been suggested to preserve acute renal vasoconstriction following cyclosporine use [11,12].

Active antibody-mediated rejection (aABMR) and chronic active antibody-mediated rejection were each identified in 20% of the cases respectively. Active aABMR has been reported to occur in up to 7% of kidney transplant patients but can be higher in HLA-incompatible transplants [13-15]. It poses a significant risk of graft loss and may lead to features of chronic antibody-mediated rejection over time [16-19]. Overall, antibody-mediated rejection may account for a substantial portion of death-censored graft loss over time.

Chronic allograft injury (CAI) was observed in 10% of the cases, reflecting the long-term deterioration of renal function in kidney transplant recipients, often influenced by immunological and non-immunological factors. The management of CAN is critical for optimizing graft survival, necessitating close monitoring and appropriate therapeutic strategies.

In addition to ATN, ABMR, and CAI, we also identified other histological patterns, including

chronic T cell-mediated rejection, acute cellular rejection, membranous nephropathy, C3 glomerulonephritis, and cortical necrosis. Each of these patterns contributes to graft dysfunction through distinct mechanisms, emphasizing the importance of early recognition for timely intervention.

The majority of patients (28 out of 30) in our study received tacrolimus-based triple immunosuppression, which has been well-documented for its efficacy in reducing acute rejection episodes. However, tacrolimus use comes with potential side effects, such as nephrotoxicity and metabolic complications, necessitating vigilant monitoring to maintain the delicate balance between immunosuppression and graft function.

Furthermore, our study focused on patients with creeping creatinine, characterized by an asymptomatic rise in creatinine with early-onset deterioration of graft function. The biopsy findings, including C4d, were described in this context. Notably, our study showed that de novo donor-specific antibodies (DSA) adversely impacted graft survival, consistent with findings from the DeKAF study [20,21]. The DeKAF study, which analyzed adult kidney transplant patients with long-term deteriorating allograft function, also revealed a high frequency of DSA and C4d, both of which increased the relative risk of graft failure.

6. CONCLUSION

Our study contributes crucial data on the spectrum of pathological findings in renal transplant recipients with an asymptomatic slow rise in serum creatinine. These findings underscore the importance of vigilant monitoring, early biopsy, and proper management of pathological conditions to enhance long-term outcomes following kidney transplantation. By identifying the underlying mechanisms driving graft dysfunction, we can develop tailored approaches for individual patients, ultimately improving the overall success of renal transplantation and the well-being of transplant recipients.

CONSENT

As per international standards or university standards, Participants' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Marta Lidia Monteverde et al: Donor-specific anti-HLA antibodies in pediatric renal transplant recipients with creeping creatinine: Prevalence, histological correlations, and impact on patient and graft survival; 2015.
   DOI: 10.1111/petr.12556
2. Mihatsch MJ, Thiel G, Ryffel B. Histopathology of cyclosporine nephrotoxicity. Transplant Proc. 1988;20:7 59-771.
3. Mihatsch MJ, Ryffel B, Gudat F. The differential diagnosis between rejection and cyclosporine toxicity. Kidney Int Suppl. 1995;52:S63-S69.
4. Paul LC, Hayry P, Foegh M, et al. Diagnostic criteria for chronic rejection/accelerated graft atherosclerosis in heart and kidney transplants: Joint proposal for the fourth alexis carrel conference on chronic rejection and accelerated arteriosclerosis in transplanted organs. Transplant Proc. 1993;25:2022.
5. Toledo Pereyra-LH, Whitten JI. Compa¬rison of the incidence and effect of ATN in the cyclosporine and ALG eras. Transplant Proc. 1988;20:910-2.
6. Chung YC, Huang MT, Chang CN, Lee PH, Lee CS, Huang TW. Prolonged nonoliguric acute renal failure associated with high-dose vitamin K administration in a renal transplant recipient. Transplant Proc. 1994;26:2129-31.
7. Canadian Multicentre Transplant Study Group. A randomized clinical trial of cyclosporine in cadaveric renal transplantation. New Eng J Med. 1983; 309:809-15.
   DOI: 10.1056/NEJM198605083141904
8. Civantos DP, Cantero AM, Marcos MR, Seijas HF, Triviño MS, Frutos MP, et al. Utility of basal regional oximetry saturation for the diagnosis of acute tubular necrosis

in the early postoperative period following kidney transplantation. Transplant Proc. 2019;51:328-33.

9. Chung YC, Lee PH, Hu RH. The outcome and delayed graft function in cadaveric renal transplants treated with low dose cyclosporine. J Formos Med Assoc. 1991; 90:975-80.
10. Toussaint C, Kinnaert P, De Pauw L. Comparison of low doses of cyclosporine with azathioprine immunosuppression during the first year following transplantation. Transplant Proc. 1986;18: 1256-8.
11. Ruggenenti P, Perico N, Mosconi L, Gaspari F, Benigni A, Amuchastegui CS, et al. Calcium channel blockers protect transplant patients from cyclosporine-induced daily renal hypoperfusion. Kidney Int. 1993;43(3):706-11.
DOI: 10.1038/ki.1993.101
12. Palmer BF, Dawidson IN, Sagalowsky AR, Sandor ZS, Lu CY. Improved outcome of cadaveric renal transplantation due to calcium channel blockers. Transplantation. 1991;52:640-5.
DOI: 10.1097/00007890-199110000-00012
13. Orandi BJ, Chow EH, Hsu A, Gupta N, Van Arendonk KJ, Garonzik-Wang JM, Montgomery JR, Wickliffe C, Lonze BE, Bagnasco SM, Alachkar N. Quantifying renal allograft loss following early antibody-mediated rejection. American journal of transplantation. 2015;15(2):489-98.
14. Gloor JM, Cosio FG, Rea DJ, Wadei HM, Winters JL, Moore SB, DeGoey SR, Lager DJ, Grande JP, Stegall MD. Histologic findings one year after positive crossmatch or ABO blood group incompatible living donor kidney transplantation. American Journal of Transplantation. 2006;6(8):18 41-7.
15. Bentall A, Cornell LD, Gloor JM, Park WD, Gandhi MJ, Winters JL, Chedid MF, Dean PG, Stegall MD. Five-year outcomes in living donor kidney transplants with a positive crossmatch. American Journal of Transplantation. 2013;13(1):76-85.
16. Thomas KA, Valenzuela NM, Reed EF. The perfect storm: HLA antibodies, complement, FcγRs, and endothelium in transplant rejection. Trends in Molecular Medicine. 2015;21(5):319-29.
17. Wiebe C, Pochinco D, Blydt-Hansen TD, Ho J, Birk PE, Karpinski M, Goldberg A, Storsley LJ, Gibson IW, Rush DN, Nickerson PW. Class II HLA epitope matching—a strategy to minimize de novo donor-specific antibody development and improve outcomes. American Journal of Transplantation. 2013;13(12):3114-22.
18. Geneugelijk K, Hönger G, Van Deutekom HW, Thus KA, Keşmir C, Hösli I, Schaub S, Spierings E. Predicted indirectly recognizable HLA epitopes presented by HLA-DRB1 are related to HLA antibody formation during pregnancy. American Journal of Transplantation. 2015;15 (12):3112-22.
19. Sigdel TK, Sarwal MM. Moving beyond HLA: A review of nHLA antibodies in organ transplantation. Human immunology. 2013;74(11):1486-90.
20. Gaston RS, Cecka JM, Kasiske BL, Fieberg AM, Leduc R, Cosio FC, Gourishankar S, Grande J, Halloran P, Hunsicker L, Mannon R. Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. Transplantation. 2010;90(1):68-74.
21. Miettinen J, Peräsaari J, Lauronen J, Qvist E Valta H, Pakarinen M, Merenmies J, Jalanko H. Donor-specific HLA antibodies and graft function in children after renal transplantation. Pediatric Nephrology. 2012;27:1011-9.

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