

Association of c4d deposition in renal allograft biopsy with morphologic features in Banff diagnosis

Amar Kumar¹, Swati Sucharita Giri^{2*}, Naveen Kumar Bariar³, Vijaya V Mysorekar⁴

¹Tutor, ^{3,4}Professor, Dept. of Pathology, Patna Medical College, Patna, Uttar Pradesh, M S Ramaiah Medical College, Bengaluru, Karnataka, India

***Corresponding Author: Swati Sucharita Giri**

Email: swatigiri2009@gmail.com

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Abstract

Introduction: Renal transplantation serves as an only form of treatment for chronic renal failure patients who became dialysis-dependent because of diseased kidney. We aim to establish the association of histopathological features of rejection with C4d immunohistochemistry results in renal transplant patients in this study.

Materials and Methods: 96 renal transplant biopsies were received from patients in department presenting with diagnosis of graft dysfunction. The Banff 2007 grading schema was used to classify histopathological features of rejection and immunostaining for C4d were done on sections.

Results: We have received 96 percutaneous allograft renal biopsies for routine histopathological evaluation with Banff scoring and C4d immunostaining. C4d immunohistochemistry in the peritubular capillaries was positive in 13 out of the 96 biopsies examined (13.5%), with focal positivity in 4 cases and diffuse positivity in 9 cases. There was significant association of peritubular capillaries C4d deposition with glomerulitis, peritubular capillaritis, interstitial fibrosis, tubular atrophy, allograft glomerulopathy, arterial fibrointimal thickening, and increase in mesangial matrix, and arteriolar hyalinosis.

Conclusion: In the present study C4d deposition in peritubular blood vessels act as a very valuable marker for the diagnosis of humoral rejection. Humoural induced graft injury if left untreated can advance to cause chronic changes like transplant glomerulopathy, atrophy of tubules along with fibrosis of interstitium, and hence leads to graft loss. Its detection in biopsies is simple and inexpensive and can help identify patients who are likely to benefit from anti-humoral therapy. This in turns stop or at least delay subsequent progression to transplant glomerulopathy or chronic rejection. It is concluded that C4d immunostaining deserves a place as a routine marker in the biopsy diagnosis of graft dysfunction and helps in guiding clinical decisions for achieving long-term renal graft survival.

Keywords: Renal allograft biopsy, C4d deposition, Banff diagnosis.

Introduction

Renal transplantation is the only form of treatment for patients who become dialysis-dependent because of diseased kidney causing chronic renal failure. Most renal allograft biopsies are done because of graft dysfunction or graft rejection. In spite of significant developments in the diagnostic modalities for renal allograft dysfunction, gold standard investigation is still the biopsy.^{1,2} The biopsy findings of renal graft predict the diagnosis of rejection and also subtype to cell or antibody mediated type and hence predicts its clinical management.

Cooperative Clinical Trials in Transplantation (CCTT) criteria followed by Banff schemes are the two most popular classification schemes that are frequently used to diagnose graft rejection.^{3,4} These classification schemes use histopathological features of acute and chronic rejection and type it. The clinical decision making and efficacy of new immunosuppressive drugs requires the correct transplant biopsy report as per the Banff diagnostic scoring system. It also provides following information such as type of rejection and its intensity along with the presence of long term changes. The specific therapeutic strategy is directly linked to this information.

Beside acute and/or chronic rejection other common factors that affect graft outcome in the late post transplantation setting are like patient tolerance with

immunosuppressant drugs and co-associated diseases, such as cardiac disease, infections, drug side effects. To guide appropriate therapy other factors beside immunological changes which help are Calcineurin inhibitor toxicity, immune-mediated injury, BK virus nephropathy, thrombotic microangiopathy, comorbid diseases like hypertension, diabetes, and recurrent disease.⁵

The usual major histopathological findings in acute cellular rejection (ACR) are an edematous interstitium and tubules infiltrated by activated T lymphocytes and monocytes and a similar infiltrate into the arterial intima and glomeruli in severe cases. To diagnosis Acute humoral rejection requires histopathological evidence of either acute tubular injury, neutrophil or mononuclear cell infiltrate into glomerulus, endothelium, or capillaries with, thrombosis of capillary along with serological presence of high circulating anti donor antibodies and diffuse C4d positivity in peritubular capillaries (PTC) are required.^{6,7}

Till yet there is no proper investigation to detect antibody-mediated rejection episodes immediately after post-transplantation period. This causes all acute rejection episodes have been misconsidered as 'cell-mediated' and treated as so. Banff classification includes characteristic histopathological and immunohistochemical changes which are seen in different forms of an antibody response thus are helpful in correct recognition of acute humoral rejection.

Antibody rejection plays a major role in renal transplant since is associated with poor renal allograft function and survival. Antibody rejection have been subclassified into hyperacute, subacute and chronic.⁸ C4, a component of the classical complement pathway which plays a major role in humoral mediated rejection split up to form C4d which in turns covalently bind to target molecules on the endothelium of peritubular blood vessels of kidney.⁹ C4d is regarded as a important marker for an antibody response and hence used as an immunohistochemical marker for a humoral mediated rejection.¹⁰ Thus recent Banff criteria has incorporated peritubular capillaries C4d immunostaining for acute humoral rejection (AHR).¹¹ Furthermore, C4d deposition has been shown to be associated with development of chronic rejection and poor graft survival.¹²⁻¹⁵

Nowadays there are effective therapeutic regimes are available for preventing the development of Acute humoral rejection and if AHR is diagnosed timely, these drugs if implemented appropriately can result in a favorable long-term graft outcome.

C4d is a bi-product of C4, a well-characterized component of the classical (antibody-activated) complement pathway.¹⁶⁻¹⁹ The breakdown product C4d, upon activation binds covalently to peritubular capillaries membrane surfaces, therefore it can be detected using immunohistochemistry.¹⁵⁻¹⁷ The correlation of C4d deposition in peritubular capillaries of renal allograft biopsies with poor graft outcome has been the subject of numerous recent publications.^{11,16} Since C4d deposition along peritubular capillaries is never seen in other conditions like native diseased and inflamed kidney, its detection seems 'transplant specific'.¹⁹ The present study is being carried out to assess the correlation of clinical features and biochemical parameters with histopathological changes and C4d expression in patients presenting with renal allograft dysfunction.

Aim of the Study

1. To evaluate the histopathological changes and expression of C4d in renal allograft biopsies in patients with graft dysfunction.
2. To establish the correlation of histopathology and C4d immunostaining results with the clinical features and biochemical parameters.

Materials and Methods

The study was conducted in the Pathology department in collaboration with the Nephrology department on the 96 percutaneous allograft renal biopsies received for routine histopathological evaluation and C4d immunostaining from January 2011 to June 2015.

Method of Collection of Data

Biopsies were received from renal transplant patients with written consent. Biopsy were taken in those patients with increased serum creatinine. Details of primary disease, history of previous transplants, duration of transplant, donor source, HLA mismatching, time from kidney transplant to biopsy, any treatment history, clinical features and the lab

findings were taken from the case files. For prospective cases, a minimum of two cores of renal tissue were received: one in 10% formalin for routine histopathology, and the other in saline for immunofluorescence. The formalin-fixed tissue was taken for conventional processing.

Histology

For routine histopathologic evaluation, paraffin sections of 4µm thickness were cut. Section were subjected to hematoxylin and eosin, periodic acid-Schiff and silver methenamine stains. Masson trichrome stain was done where necessary. The histopathological features were classified according to the Banff 2007 grading schema. The section which has 10 glomeruli or more with at least two arteries was regarded as adequate. However, biopsies having 7 glomeruli and one artery are also accepted. In addition to these, other features were also noted which are independent of rejection like glomerular disease, interstitial diseases, drug toxicity and infections.

C4d Staining

Paraffin-embedded sections are stained with C4d immunostaining (by polymer-Horseradish Peroxidase (HRP) technique. The polyclonal antiserum used to C4d is from Biogenex, India. Briefly, the procedure was as follows: 4µm sections were cut from the paraffin block and taken on a glass slide coated with adhesive (Polylysine). Antigen retrieval was done in a microwave oven by tris- EDTA buffer, followed by peroxidase block and protein block and incubation with primary antibody for 1 hour, enhancer for 30 min and polymer-HRP for 30 min. Diaminobenzidine (DAB) chromogen is used to visualized Antigen antibody complex and then counterstained with Harris hematoxylin. Positive control were taken from biopsies of patients having membranous nephropathy with glomerular positivity and negative control were taken from peritubular capillaries in the same.

Inclusion Criteria

Allograft biopsies from all patients with graft dysfunction were studied.

Exclusion Criteria

1. Biopsies which were unsatisfactory according to Banff criteria, i.e., containing less than 7 glomeruli and no arteries.
2. Biopsies containing only fibrotic or necrotic parenchymal regions without sufficient viable tissue for accurate evaluation

Statistical Analysis

The following methods of statistical analysis were used in this study. Data was entered in Microsoft excel and analysed using SPSS (Statistical Package for Social Science, Ver.10.0.5) package. The results were presented in number and percentage for dichotomous data in Tables and Figures. Chi-square (χ^2) test of significance were used for comparison of Proportions.

Result

The present study was conducted on 96 renal allograft biopsies obtained from renal transplant patients presenting

with graft dysfunction demonstrated by raised levels of serum creatinine above their baseline value. These patients had symptoms of nausea, fever, anorexia, dyspepsia, burning micturition, proteinuria and generalized weakness. Majority of the patients were male gender (80.2%) and 17 (19.8) were females. However, there was no correlation of gender with age in any age group. Most of the patients requiring transplantation had end stage renal disease (ESRD) with no specific evidence to suggest the primary renal disease. Among the total number of cases in the present study, in majority 65 (67.7%), the donors were living related and 16.7% were living unrelated and rest 15.6% were cadaveric.

Serum creatinine value was estimated at the time of biopsy after transplantation as a routine protocol. Out of 96 patients, 43 (44.8%) of the patients had serum creatinine value ≥ 2.3 mg/dl.

57.3% of patients were given Maintenance therapy (Triple therapy -Calcineurin blockers (cyclosporine or Tacrolimus) combined with an anti-proliferative agent Mycophenolate mofetil and steroids.) as the immunosuppressive regimen after transplantation while the rest 42.7% were given Induction therapy-Polyclonal antibody preparations (Basliximab/Rituximab/Anti thymocyte globulin) were given followed by Triple therapy or Maintenance therapy.

Out of the 96 cases studied, 38 (39.6%) had histopathological features suggestive of graft rejection, while 58 (60.4%) had features which did not suggest immunological rejection.

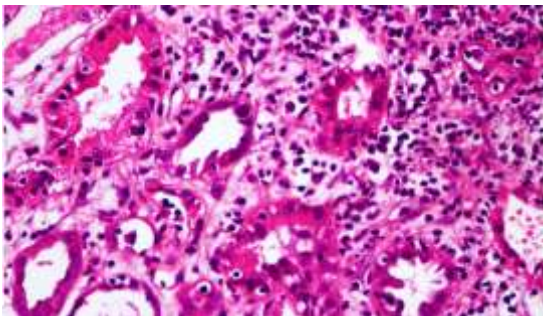


Fig. 1: Showing lymphocyte- predominant infiltrate in the lining epithelium of tubular epithelial cells (tubulitis) and in the interstitium (H&E X200)

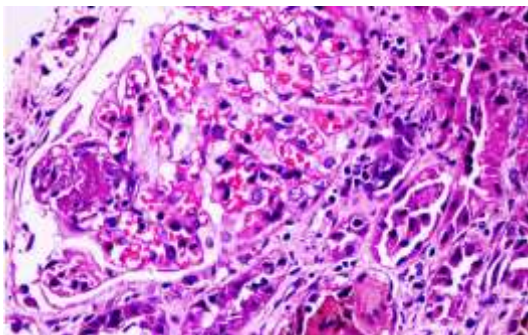


Fig. 2: Showing glomerulus having neutrophilic inflammatory infiltrate and mesangiolysis (H&E X200)

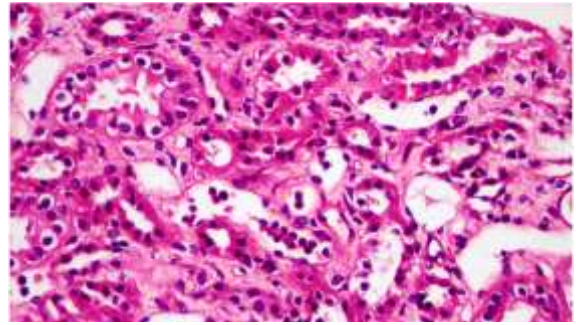


Fig. 3: Showing peritubular capillaries having luminal inflammatory cells, mainly mononuclear cells (H&E X200)

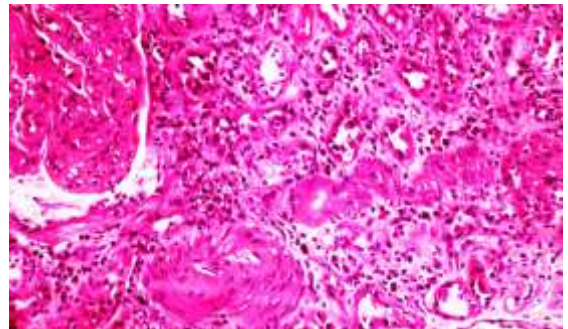


Fig. 4: Showing a large artery having fibrointimal expansion causing 30% luminal reduction (H&E X100)

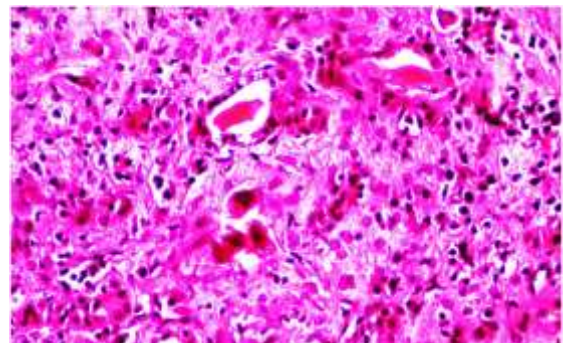


Fig. 5: Showing interstitial fibrosis involving more than 50 per cent of cortex (H&E X200)

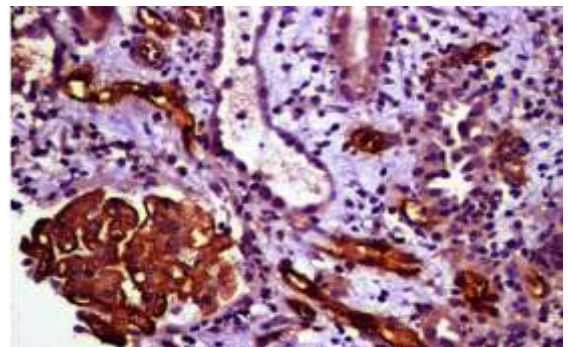


Fig. 6: Showing diffuse positivity for C4d in the peritubular capillaries (more than 50%). Glomerular positivity is also noted (IHC X200)

Immunohistochemistry Results

C4d immunostaining as defined by Banff score in peritubular capillaries was positive in 13 out of the 96 biopsies examined (13.5%), with focal positivity in 4 cases and diffuse positivity in 9.

Interstitial inflammation was seen in 49 of the 96. Tubulitis was seen in 21 of the 96 (21.9%) biopsies examined. Among the biopsies 12 cases shows glomerulitis. Majority of biopsies (97.9%) showed no arterial inflammation. Two cases showed arterial inflammation of intima occupying less than 25% of the luminal area. Among the 96 biopsies 12 (12.5%) showed features of peritubular capillaritis.

Interstitial fibrosis was seen in 31 of the 96 (32.3%) biopsies examined. Of these, 13 cases were finally grouped under the category "Interstitial fibrosis and tubular atrophy (IFTA)", while in the other cases the interstitial fibrosis was just a part of the process of interstitial nephritis, not due to immunological rejection. Tubular atrophy was seen in 33 of the 96 (34.4%) biopsies examined. Among the 96 biopsies, 4 (4.2%) showed features of allograft glomerulopathy. Arterial fibrointimal thickening was found in 35 out of the 96 biopsies studied (36.4%). 38 (39.7%) of the 96 cases showed increase in the glomerular mesangial matrix in the biopsy sections. Arteriolar hyalinosis was seen in 36 out of the 96 biopsies studied (37.5%).

C4d positivity was taken as the criterion for the diagnosis of acute and chronic active antibody mediated rejection. Among the Banff acute rejection score, No significant correlation of C4d immunostaining pattern with interstitial inflammation was found. No significant correlation of C4d immunostaining pattern with tubulitis was found. Majority of cases which showed g2 glomerulitis have diffuse C4d positivity i.e. > 50%. Out of 4 cases of glomerulitis less than <25%, 3 were negative for C4d and one case showed diffuse positivity. There was significant correlation of glomerulitis with C4d positivity ($p<0.001$) and 8 cases of glomerulitis seen in 25-75%, 1 show c4d focal and 5 shows diffuse positivity. No significant correlation of C4d immunostaining pattern with arterial inflammation was found. Out of the 5 cases showing ptc more than 10% of peritubular capillaritis, 2 were diffusely positive for C4d and out of 7 cases of ptc 2, 4 were diffusely positive. There was significant correlation of ptc with C4d positivity ($p<0.001$).

Among Banff Scoring Categories for Chronic Changes, Out of 14 cases of interstitial fibrosis seen in 6-25% of cortex, 1 showed focal and 2 showed diffuse C4d positivity. 13 cases were of interstitial fibrosis seen in 26 -50% of cortex, out of which 7 were positive for C4d (1 focal positive and 6 diffusely positive). Biopsies with interstitial fibrosis seen in >50% of cortex were all negative for C4d. There was significant correlation of interstitial fibrosis with C4d positivity ($p<0.001$). Out of 14 cases of tubular atrophy seen in <25% of cortex, 1 showed focal and 1 showed diffuse C4d positivity. 13 cases were of 26 -50% of cortex, out of which 8 were positive for C4d (1 focal positive and 7 diffusely positive). All 6 biopsies with >50% of cortex were

negative for C4d. There is significant correlation of tubular atrophy with C4d positivity ($p<0.001$).

There was significant correlation of allograft glomerulopathy with C4d positivity ($p<0.001$). The single case of allograft glomerulopathy seen in 26-50% of peripheral capillaries with double contours, in the most severely affected glomerulus was diffusely positive for C4d. 3 cases had allograft glomerulopathy >50% of peripheral capillaries with double contours, in the most severely affected glomerulus, of which 1 was C4d negative and 2 showed diffuse positivity. There was significant correlation of arterial fibrointimal thickening with C4d positivity ($p<0.001$). Out of 17 cases showing <25% narrowing of luminal area in the most severely affected artery, 15 were negative and 2 were diffusely positive for C4d. 10 cases which had cv score show 26-50% narrowing of luminal area in most severely affected artery, of which 4 were C4d negative and 6 were positive with 1 showing focal and 5 shows diffuse positivity. Out of 8 cases of >50% narrowing of luminal area in the most severely affected artery, 7 were negative and 1 was focally positive. Out of the 11 cases of mesangial matrix increase in % of glomeruli, 10 were negative and 1 was focally positive for C4d. Out of 16 cases of mesangial matrix increase in % of glomeruli, 2 were focally positive and 3 diffusely positive for C4d. Out of 11 cases of mesangial matrix increase in % of glomeruli, 5 were diffusely positive and 1 was focally positive, while 5 were negative for C4d. There was significant correlation of increase in mesangial matrix with C4d positivity ($p<0.001$). Out of 12 cases of 1 number of non circumferential arteriolar hyalinosis, 2 were diffusely positive for C4d and 10 were negative. 5 cases were of >1 Non circumferential arteriolar hyalinosis, out of which 4 were negative for C4d and 1 focally positive. Out of 19 biopsies with ≥ 1 Circumferential arteriolar hyalinosis, 12 were negative and 7 were positive for C4d, 2 focally and 5 diffusely positive. There was significant correlation of arteriolar hyalinosis with C4d positivity ($p=0.008$).

No significant correlation of C4d immunostaining result with serum creatinine or gender of the patients or with the immunosuppressive regimen received was found or with donor source and number of days from transplant was found.

Table 1: Association between the individual histopathology diagnosis and C4d immunostaining pattern

Histopathology diagnosis	C4d finding			Total
	Negative	Focal 10-50%	Diffuse 50%	
Normal	13	0	0	13
	100.0%	0%	0%	100.0%
C4d + Acute Antibody Mediated Rejection	0	1	3	4
	0%	25.0%	75.0%	100.0%
C4d + Chronic Active Antibody Mediated Rejection	0	3	6	9
	0%	33.4%	66.6.0%	100.0%
Borderline changes suspicious of acute rejection	10	0	0	10
	100.0%	0%	0%	100.0%
Acute cellular (T cell mediated) rejection	2	0	0	2
	100.0%	0%	0%	100.0%
Interstitial Fibrosis And Tubular Atrophy	13	0	0	13
	100.0%	0%	0%	100.0%
Acute Tubulointerstitial Nephritis	16	0	0	16
	100.0%	0%	0%	100.0%
Chronic Tubulointerstitial Nephritis	11	0	0	11
	100.0%	0%	0%	100.0%
Polyomavirus infection	2	0	0	2
	100.0%	0%	0%	100.0%
Acute tubular injury	25	0	0	25
	100.0%	0%	0%	100.0%
Cortical necrosis – Partial/ Total	5	0	0	5
	100.0%	0%	0%	100.0%
Calcineurin inhibitor-induced toxicity	6	0	0	6
	100.0%	0%	0%	100.0%
Mixed opportunistic infection	1	0	0	1
	100.0%	0%	0%	100.0%
Associated glomerular disease	1	0	0	1
	100.0%	0%	0%	100.0%

Table 2: Number of cases showing individual parameters of Banff scoring and its association with C4d immunostaining pattern. (P value)

	Features seen in number of biopsy (n=96)	Association between various parameters of Banff scoring and C4d immunostaining pattern. (P value)
Interstitial inflammation	49	0.216 (Not significant)
Tubulitis	21	0.888 (Not significant)
Glomerulitis	12	<0.001 (significant)
Arterial inflammation	2	0.136(Not significant)
Peritubular capillaritis	12	<0.001 (Significant)
Interstitial fibrosis	31	<0.001 (Significant)
Tubular atrophy	33	< 0.001 (Significant)
Allograft glomerulopathy	4	<0.001 (Significant)
Arterial fibrointimal thickening	35	< 0.001 (Significant)
Mesangial matrix increase	38	< 0.001 (Significant)
Arteriolar hyalinosis	36	0.008 (Significant)

Table 3: Association (P value) of acute Banff scoring parameters with C4d positivity

	Glomerulitis (g)		Peritubular capillaritis (ptc)		Tubulitis (t)		Interstitial inflammation (i)		Arterial inflammation (v)	
	C4d +	C4d-	C4d +	C4d -	C4d +	C4d-	C4d +	C4d -	C4d +	C4d -
Maiyyedi et al ⁹⁷	< 0.01	-	0.01	-	NS	-	NS	-	NS	-
Nowotny et al ¹⁰⁶	0.02	-	<0.001	-	0.99	-	NS	-	0.04	-
Nickeleit et al ⁷⁶	0.0001	-	NS	-	NS	-	NS	-	0.004	-
Regale et al ⁹⁶	0.02	-	0.001	-	0.04	-	NS	-	NS	-
Kieran et al ⁹⁵	0.0001	-	0.0001	-	0.0001	-	0.0001	-	0.03	-
Ranjan et al ¹⁰²	NS	-	<0.005	-	NS	-	NS	-	NS	-
Kulkarni et al ¹⁰⁵	NS	-	0.02	-	0.001	-	0.012	-	0.15	-
Present study	<0.001	-	<0.001	-	0.888	-	0.216	-	0.136	-

NS = not significant

Table 4: Association (P value) of chronic Banff scoring parameters with C4d positivity

	Interstitial fibrosis (ci)		Tubular atrophy		Allograft glomerulopathy		Arterial fibrointimal thickening		Mesangial matrix increase		Arteriolar hyalinosis	
	C4d +	C4d-	C4d +	C4d-	C4d +	C4d-	C4d+	C4d-	C4d+	C4d-	C4d+	C4d-
Kieran et al ⁹⁵	0.01	-	0.01	-	<0.001	-	0.01	-	0.0001	-	0.8	-
Regele et al ⁹⁶	NS	-	0.01	-	0.0001	-	NS	-	NS	-	0.07	-
Ranjan et al ¹⁰²	NS	-	NS	-	0.05	-	NS	-	NS	-	NS	-
Present study	<0.001	-	<0.001	-	< 0.001	-	<0.001	-	<0.001	-	0.008	-

NS = not significant

Discussion

The rate of C4d positivity obtained in the present study was similar to that obtained by Mengel et al,²⁰ Hyeon Joo Jeong et al²¹ and Kieran et al.²² In the present study, C4d staining and peritubular capillaritis showed the strongest association. Glomerulitis also showed significant association with C4d positivity ($P < 0.001$). These findings were comparable to those of Kieran et al,²² Nowotny et al,²³ Regale et al,²⁴ and Maiyyedi et al.²⁵ Studies done by Ranjan et al²⁶ and Kulkarni et al²⁷ showed significant association between peritubular capillaritis and C4d positivity, but no significant association between glomerulitis and C4d positivity. In contrast, Nickeleit et al²⁸ found no significant association of peritubular capillaritis with C4d positivity.

Our findings are comparable to those of Maiyyedi et al²⁵ and Ranjan et al,²⁶ where no significant association of C4d was found with tubulitis, interstitial inflammation and arterial inflammation. This suggests that C4d does not have a prominent role in cell-mediated rejection. Kieran et al²² had significant association of C4d positivity with interstitial inflammation and arterial inflammation.

In the present study, among the acute rejection score, C4d staining and peritubular capillaritis showed the strongest association. Glomerulitis also showed significant association with C4d positivity ($P < 0.001$). These findings were comparable to those of Kieran et al,²² Nowotny et al,²³ Regale et al,²⁴ and Maiyyedi et al.²⁵ Studies done by Ranjan et al²⁶ and Kulkarni et al²⁷ showed significant association between peritubular capillaritis and C4d positivity, but no significant association between glomerulitis and C4d positivity. In contrast, Nickeleit et al²⁸

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Among Banff Scoring Categories for Chronic Changes, Kieran et al²² found that interstitial fibrosis, tubular atrophy, allograft glomerulopathy, arterial fibrointimal thickening and mesangial matrix increase were associated with C4d positive biopsies, a finding similar to that in the present study. Their findings differentiated from those of Regele et al²⁴ and Ranjan et al²⁶ who found no significant correlation of interstitial fibrosis, arterial fibrointimal thickening and mesangial matrix increase, with C4d immunostaining.

All the three above-mentioned studies have no significant association of arteriolar hyalinosis with C4d, unlike the present study. In our study there was strong association between C4d positivity and all the above-mentioned features of chronicity, suggesting that antibody mediated mechanism could have a role in the development of chronic rejection, as stated by Kieran et al.²²

Conclusion

Graft dysfunction in a renal transplant patient could be due to graft rejection as well as other causes such as acute tubular injury, cortical necrosis, graft infection, calcineurin inhibitor-induced toxicity, or recurrence of the primary disease. Thus, a detailed evaluation and Banff scoring of each histopathological parameter in the kidney biopsy plays a key role in determining the cause of graft failure and

planning its management. C4d deposition in peritubular capillaries plays a key role in confirming the diagnosis of antibody-mediated rejection in the present study. Antibody mediated graft injury if left untreated has the potential to cause chronic rejection which in turn leads to graft loss. Acute humoral rejection detection in biopsies is simple by doing C4d immunostaining. It is inexpensive procedure and can help those patients who are likely to benefit from anti-humoral medications. Prompt treatment for antibody rejection by these drugs may prevent and delay development of chronic rejection. It can be concluded that C4d immunostaining should be used in biopsy as a routine marker in the diagnosis of graft dysfunction and helps in guiding clinical decisions for achieving long-term graft survival.

Conflict of Interest: None.

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