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Pathological Study on Renal Allograft Biopsies - Evaluation of Rejection Cases

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Abstract: ***Renal transplantation is one of the life-saving modality of treatment for end-stage renal diseases[1]. Graft rejection and the complications of immunosuppressive therapy continue to be the major causes for allograft loss. The clinical and morphological features on allograft biopsy associated with rejection remains to be learned much[2]. Consecutive 50 cases whose renal biopsies were done from January 2010 to June 2012 at Aiims, New Delhi were selected randomly and analyzed in respect to clinical, histological and their follow up for 6 months.Out of 50 biopsies, 38 were found to have rejection and among those 19 (38 %) showed combined acute cellular(ACR) and chronic rejection(CR), 11 (22%) showed only CR and 8 (16%) showed only ACR. 12 biopsies (24%) were found as non-rejection as per the Banff'2003 and CCTT criteria.[3,4,5]In our study clinical features alone neither diagnostic nor predictive of acute rejection[6]. Histological evaluation is considered as most definitive and reliable method for predicting and to diagnose the rejection.[7,8]Even though the grading of ACR is similar with both Banff and CCTT criteria, Banff systemfound to be valuable in predicting sub clinical, humoral rejection and early chronic rejection.***

Keywords: Banff, CCTT, acute, chronic,cellular and humoral rejection

1. Introduction

More than 30000 renal transplants are performed annually worldwide[9]. The most common indications for renal transplantation are diabetes, hypertension, polycystic kidney disease and the various types of glomerular diseases, most commonly IgA nephropathy[1]. Graft survival and functioning is most important for success of transplantation.However the short-term survival rates have considerably improved over the past two decades.[10]Prevention of chronic rejection still remains a major hurdle in improving long-term allograft survival.[11]The complex intracellular cascades producing T and B cell activation and cross talk have been only partially defined. Substantial gaps in our knowledge remain, particularly about events that determine the type of immune response initiated by a given patient toward his allograft and about how to redirect the mechanisms from allo-aggression to allo-tolerance.

2. Literature Survey

Carl Williamson published the first histopathological pictures of allograft rejection in 1926. He described 'marked lymphocytic infiltration' and 'intense glomerulitis' and attributed graft loss to the 'atypical glomerulonephritis'[12].Clinically evident acute rejection now accounts for 11% to 16% of graft failures in the first year and 7% to 11% of failures after the first year. It affects 12% to 18% of recipients of living donor kidneys and 14% to 30% of deceased donor kidneys in the first 6 months.[13]

The classical clinical features are an abrupt rise in serum creatinine that progresses over several days, a declining urine output, weight gain, fever, malaise, graft tenderness and swelling. Rarely acute rejection can present with the nephrotic syndrome[14].Two types of histological classification and categorizations of acute rejection have been proposed. One is Banff classification which was recently modified and the other one proposed by National Institutes of Health (NIH), CCTT (cooperative clinical trials in transplantation).

For the diagnosis of cellular rejection, well-defined histological criteria were laid down under the Banff system[4, 16] in 1993 and were further revised in 1997, 2003[17].It is a system for classification and grading rejection in order to achieve uniformity in histopathological assessment of renal graft biopsies. It was the result of discussions among an international group of renal pathologists, nephrologists and transplant surgeons[17].In view of these observations Banff (1997) classification was revised in 2003[5]and 2005 incorporating morphological criteria, supported by immuno-pathological criteria and serological evidence for acute humoral rejection.

Morphologically the changes are classified[5] into,

- Borderline
- Antibody mediated rejection
- Acute/active cellular rejection
- Chronic/sclerosing allograft nephropathy

'CCTT' (Cooperative clinical trials in transplantation) criteria for acute cellular rejection considered superior to 'Banff' in predicting graft survival and is also simple and easily reproducible.

Acute humoral rejection (AHR) has been divided into three types based on light microscopy into three types[3, 18]-acute tubular injury, neutrophils in peritubular capillaries and fibrinoid necrosis of arteries. Biopsies that meet the criteria for both AHR and ACR are considered to have both forms of rejection. AHR may be manifested only by acute tubular injury without other evidence of rejection (10%). AHR has markedly poorer prognosis[19] (27 to 40 percent one year graft loss) than ACR without a humoral component (3 to 7 percent one year graft loss).

3. Methods / Approach

All the allograft biopsies between January 2010 and January 2012 were included. All the biopsies were indicated and performed for the diagnosis of graftdysfunction. Cases with adequate tissue for both routine histological staining and Immunohistochemical staining were selected randomly. Details of primary disease, duration of transplant, type of donor, presenting features and the laboratory data were taken from case files. The light microscopic features were evaluated in every biopsy using haematoxylin and eosin, periodic acid-Schiff and silver Methenamine stains. All the slides on H&E were analyzed under light microscope for confirming the original diagnosis and to characterize the type and grade of rejection using Banff 2003 and CCTT criteria[4,5,16](REFER TO FIGURES 2 TO 7)

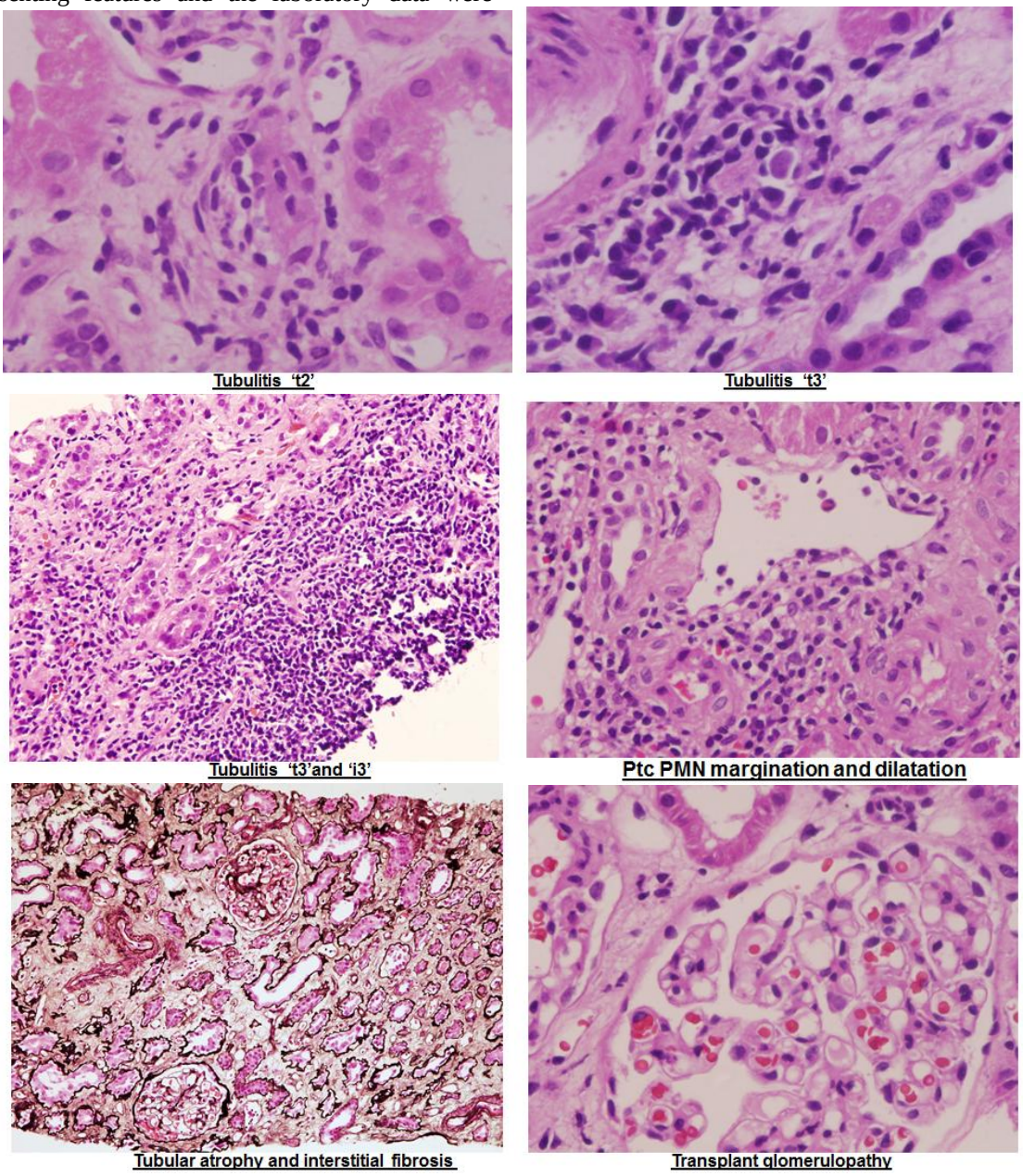

Figure 2 to 7: H&E and Silver Methanamine Staining

4. Results and Discussion

Our study analyzed 50 cases of renal transplant biopsies, retrospectively and prospectively with respect to clinical, biochemical and histological parameters along with their response to treatment on follow up.Comparisons of the various clinical and histological parameters were done by PARAMETRIC TESTS (CHI- SQUARE and FISCHER EXACT T TEST).

Out of 50 cases in this study, 43 cases were male (86 percent) and 7 cases were female (14 percent) with a male to female ratio was 6.1:1.Age distributions ranged from 17 to 51yrs with a mean and standard deviation of 32.46 ± 8.8 yrs. Majority of our cases (50%) were in the age group of 21-35years.39 patients (78 percent) had live related donors (LRD), 10 cases (20 percent) had live unrelated donor (LURD) and one (2 percent) had cadaver donor (CD).

The onset of graft dysfunction observed in our study, ranged from as early as 7 days to 5 years post-transplant period.

Majority of graft dysfunction occurred after 6months of post-transplant period. It showed highly uneven distribution.ACR occurred even after 2 years and the CR occurred even after few months. So the graft dysfunctions should not be classified either as acute or chronic rejection based on the duration.

In this study, most common indication for transplantation was Chronic Glomerulo-Nephritis (CGN)-65%, Diabetic Nephropathy -52%. Rest of other causes includes hypertensive nephropathy, focal segmental glomerulosclerosis, chronic interstitial nephritis and adult polycystic kidney disease. Also we observed that the level of serum creatinine was not correlating with the histological diagnosis of rejection. Some of the cases were shown high level of serum creatinine biochemically but their histological diagnosis did not show any evidence of rejection.

All the 50 cases were graded according to Banff 2003 and CCTT criteria[3,4,16] for both acute and chronic rejection. Among the 50 cases 38 cases (76%) were found to have rejection, in the form of Acute Cellular Rejection, Chronic Allograft Nephropathy and combined rejection. 12 cases (24%) were found to have no rejection in our study(figure 1& 2). The inter-observer reproducibility of the present Banff criteria is improved after the incorporation of the CCTT criteria[20,21]

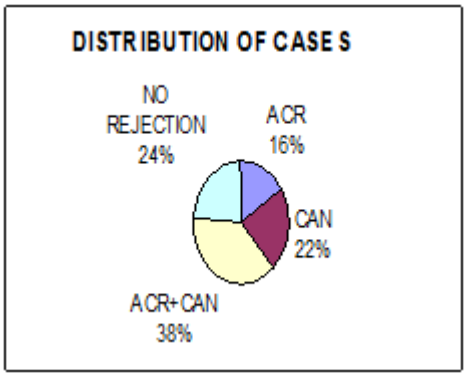

Figure 1: Distribution of cases

Table 1: Histological classification of cases

BANFF ACR Grade	No. of Cases (n=50) (%)	CCTT ACR Grade	No. of cases (n=50) (%)
0	23(46)	0	23(46)
Borderline	4(8)	I	6(12)
Ia	1(2)	II	21(42)
Ib	1(2)		
IIa	9(18)		
IIb	12(24)		

On applying Banff CAN criteria, it shows highly unequal distribution. 20 cases (40 percent) were found to have no rejection. 16 cases (32 percent) were found to have chronic allograft nephropathy of grade I.

In a Canadian series of 184 protocol biopsies, agreement rate for rejection was 74 percent but there was only 43 percent agreement on the suspicious cases[22,23]. A recent European series reached similar conclusions[22,23]. CCTT has a 91% agreement rate on acute rejection[20]. Even experienced pathologists do not reproducibly score certain Banff features. Among a group of 21 European pathologists, the agreement rate was poor for all of the acute Banff scores (t, i, v, g) in transplant biopsy slides[23].

CCTT criteria was superior to Banff in predicting graft survival and also simpler and easily reproducible. Threshold for diagnosing acute cellular rejection was comparatively less in CCTT criteria than the Banff 2003 criteria[20]. In our study 4 cases which were diagnosed as grade I acute cellular rejection, were actually placed in 'suspicious' or borderline category according to Banff 2003 criteria[5]. The rationale for the term 'suspicious' or borderline is that many but not all of these cases are indeed rejection; also it draws attention to the need for further studies to distinguish those cases of rejection from those that will resolve spontaneously[24,25].

Two large studies[24,25] have shown that 75 to 88 percent of patients with suspicious or borderline rejection improve renal function with increased immunosuppression, comparable to response rate in type I rejection (86 percent). In follow up biopsies 1 month later, the histology often progressed to florid rejection (33 percent to type I; 46 percent to type II or III). Others find that a minority (28 percent) untreated suspicious cases progress to frank acute rejection in 40 days[24,25].

Arterial lesions are considered to be one of the strong prognostic significance either individually or in combination and it alone doubled the rate of graft loss[26,27].In our study - 12 out of 50 cases (24 %) showed features of arteritis and dilatation of peri-tubular capillaries, neutrophillic margination. These cases also showed high creatinine value and the workup for humoral rejection should be followed up for those cases. Recognition of humoral rejection may be problematic in biopsies with dense mononuclear inflammatory infiltrates that fulfill criteria for acute rejection by the Banff schema[17]

5. Conclusion

CCTT criteria are simple and reproducible but the threshold for diagnosing acute cellular rejection was comparatively less than the Banff 2003 criteria.Further studies needed to distinguish those cases of borderline (suspicious) or subclinical rejection from those that will resolve spontaneously. Recognition of humoral rejection may be problematic in biopsies with densely cellular inflammatory infiltrate. All the transplant biopsies should be screened for humoral component irrespective of the rejection status.

6. Future Scope

All the transplant biopsies should be studied and classified according to the latest immuno-pathological criteria proposed by BANFF. C4d immuno-staining should be done in all the transplant biopsy workup as a routine for the detection of coexisting humoral component irrespective of the rejection grade.

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