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ORIGINAL ARTICLE

Correlation between the Banff 97 classification of renal allograft biopsies and clinical outcome

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Abstract The 1997 fourth Banff meeting revised the consensus for describing transplant biopsies. We have conducted a retrospective analysis of biopsies correlated between the Banff 97 classification and clinical outcome. The patients ($n = 149$), who had a total of 404 biopsy-proven rejections, were assessed and the biopsies taken from these patients were re-examined and classified according to the Banff 97 classification. Morphological changes in the glomeruli (g), interstitium (i), tubules(t), and arterial vessels (v) were scored. Severity of acute rejection was statistically associated with unresponsiveness to anti-rejection treatment ($P < 0.0001$) and predicted an increased risk of graft failure ($P < 0.05$). Each quantitative criterion (g, i, t, and v) was also statistically associated with unresponsiveness to anti-rejection treatment. Mean serum creatinine levels were significantly higher in the groups graded Banff 97 type I–III after 1 and 2 years of follow-up. The Banff 97 classification correlated with reversibility of rejection episodes and long-term graft survival.

Keywords Banff 97 classification · Acute rejection · Graft survival · Reversibility of renal function

Introduction

Rejection remains a significant problem following renal allotransplantation and, although powerful anti-rejection therapy is available, its unguided use is associated with significant morbidity and mortality [1]. Needle core biopsy for conventional histological examination remains the technique of choice for the diagnosis of rejection [2], but in the past the interpretation of histological appearance was subjective. In 1991, amid this

confusion, a group of pathologists, nephrologists, and surgeons met in Banff, Canada, to standardize a classification for the histological appearances and definitions of chronic and acute allograft rejection. After 2 years of correspondence and revisions of the text, the final article was published in 1993 [3]. This arrangement allowed for the classification of renal allograft pathology and acute rejection. The goal of the Banff classification of renal allograft rejection was a schema in which a given biopsy grading would imply a prognosis for the therapeutic response of long-term function [3]. Thus, we previously reported correlations between the Banff 93–95 classification and reversal of acute allograft rejection and long-term graft survival [4, 5]. Although the Banff schema has good reproducibility and is clinically relevant, it is recognized that there is room for improvement. Recently, it has been revised to the Banff 97 working classification [6] and is now in register with the CCTT classification [7]. Rejection episodes are common, and the presence of the vascular type of rejection has been found to be the most important predicting variable for both early and late graft loss in a single-center cohort study [8]. In view of recent studies which provide evidence that vasculitis has implications for response to therapy and/or graft survival [1, 7], the Banff 97 classification focuses on the type of rejection. Type I constitutes tubulointerstitial rejection without arteritis, type II vascular rejection, and type III severe rejection [6]. It was emphasized from the outset that the development of the standardized schema was only the first step and that the clinical implications needed to be proven through further studies. However, such studies related to Banff 97 remain scarce.

In the present single-center study, we retrospectively looked for distinct histological changes in renal core biopsy specimens from transplant recipients. The aim of this paper is to examine the correlation between histological findings and clinical outcome, using the new, revised Banff 97 classification.

Patients and methods

Patients

This study was based on data collected from Osaka University. The study sample consisted of 149 patients who underwent transplantation between October 1986 and December 1999. Baseline immunosuppression was achieved with triple- or quadruple-drug therapy. Triple-drug therapy consisted of cyclosporine (or tacrolimus) at an initial oral dose of 6–8 mg/kg per day (or 0.2–0.3 mg/kg per day) adjusted according to trough blood level, mizoribine (or azathioprine), and prednisolone. Quadruple-drug therapy consisted of cyclosporine (or tacrolimus), mizoribine (or azathioprine), prednisolone, and antilymphocyte globulin, as described previously [4].

Acute rejection was defined using the following clinical and biochemical criteria: elevation in baseline of serum creatinine, reduction in urine output, and response to anti-rejection therapy. First rejection episodes were treated with pulsed intravenous methylprednisolone, continuing rejection with Orthoclone OKT3 monoclonal antibodies or deoxyspergualin. Renal allograft biopsies were performed when acute rejection was suspected (243 biopsies) and a large amount of proteinuria was recognized (22 biopsies). Non-episode biopsies (139 biopsies) were also included in this study. The biopsies with signs of rejection were carried out as early as possible (almost within 1 or 2 days). The rate of persistent/recurrent rejection was 9.5% (11/115) in recurrent biopsies. The biopsies taken from these patients, which had originally been reported according to the Banff 93–95 classification [3], were re-examined and classified according to the Banff 97 classification [6]. Morphological changes in the glomeruli (g), interstitium (i), tubules (t), and arterial vessels (v) were scored semi-quantitatively from 0 to 3.

Clinical data

The following data were obtained from the review of case notes: recipient age and sex, HLA mismatch, total ischemic time, donor status (age, cadaveric vs living), number of acute rejection episodes, and timing of allograft biopsies. The outcome measures considered were clinical recovery from acute rejection, graft failure, and serum creatinine at 1 and 2 years. Graft failure was defined by permanent return to dialysis.

Biopsy

We used a Biopty gun (C.R. Bard, Covington, Ga.) with a 16 gauge true-cut needle. All biopsies were performed under ultrasound guidance. No significant complications were seen in any of the biopsies. All biopsy specimens were stained with hematoxylin-eosin, periodic acid-Schiff, periodic acid-methenamine silver reagent and Masson trichrone. The biopsy specimens were read by at least two observers. For each patient, the biopsy found to be the most severely abnormal was selected.

Recovery from rejection

Recovery from rejection was assessed by comparing the level of serum creatinine (Cr) measured after completion of anti-rejection treatment (post-Cr) to the stable baseline Cr prior to the rejection episode (pre-Cr). A return of post-Cr to that of pre-Cr was considered a complete response of recovery from rejection (CR). A partial response (PR) was defined as a post-Cr improvement following anti-rejection treatment, but without achieving pre-Cr values. Rejection was considered irreversible (IR) if the post-Cr was not decreased or if loss of graft function occurred. Rejections occurring during acute tubular necrosis were excluded.

Statistical analysis

One-way ANOVA for parametric values was used to compare each group. The χ^2-test was used to compare categorical data. Graft survival estimates were compared using the Kaplan-Meier method and log-rank analysis. All values are given as mean ± standard deviation (SD), and all results were considered to be of statistical significance with $P < 0.05$.

Results

Demographics of patients

The mean recipient age was 33.7 years (range: 3–57 years) and 96 patients (64.4%) were male. The mean

donor age was 51.3 years (range: 7–73 years). One hundred and twenty-three grafts (82.6%) were from living donors and 26 from cadaveric donors. The mean number of mismatches at the HLA A-B loci was 1.5. One hundred and sixteen patients (77.9%) had a single mismatch and four patients had two mismatches at the DR locus. The median time of renal biopsies was 31.0 days after transplantation (range: 1–3368 days). There was no correlation between Banff 97 type of acute rejection and recipient and donor age, donor source (cadaveric vs living), HLA mismatch number, total ischemic time, or timing of allograft biopsies (Table 1).

Grading of acute rejection

According to the Banff 97 classification, the 149 transplant patients with biopsy-proven rejection were graded to the following categories: 26 (17.4%) borderline change (BC), 58 (39.0%) type IA, 23 (15.4%) type IB, 27 (18.1%) type IIA, 7 (4.7%) type IIB, 8 (5.4%) type III rejection (Table 1).

Graft survival after renal transplantation in each Banff 97 category

Outcome in terms of graft survival for patients with biopsies in each Banff category is shown in Fig. 1. Patients whose biopsies were graded type IIB and III according to Banff 97 had a very poor outcome, whereas more than 60% of the patients in the BC, type IA, IB, and IIA rejection groups significantly had functioning grafts at 10 years after transplantation compared with type IIB and III.

Table 1 Demographics of patients (*BC* borderline change, *N.A.* not applicable, *N.S.* not significant)

Type	BC	IA	IB	IIA	IIB	III	*P*-value
Number of patients	26	58	23	27	7	8	
Recipient age	37	34	32	31	33	38	N.S.
Donor age	54	55	57	51	60	52	N.S.
HLA mismatch number							
HLA-A	0.6	0.6	0.5	0.6	0.7	1.1	N.S.
HLA-B	0.9	0.8	0.9	1.0	0.9	1.0	N.S.
HLA-DR	0.7	0.9	0.7	0.8	0.7	1.0	N.S.
Total ischemic time							
Living donor (min)	49	51	51	43	53	38	N.S.
Cadaveric donor (min)	346	629	390	584	N.A.	322	N.S.
Living/Cadaveric	19/7	50/8	22/1	20/7	7/0	5/3	N.S.
Biopsy timing (days)	62	35	23	25	11	28	N.S.

Recovery of graft function after renal transplantation in each Banff 97 category

Figure 2 shows that recovery from rejection correlated with the Banff 97 classification after acute rejection episodes. Most patients whose biopsies showed BC,

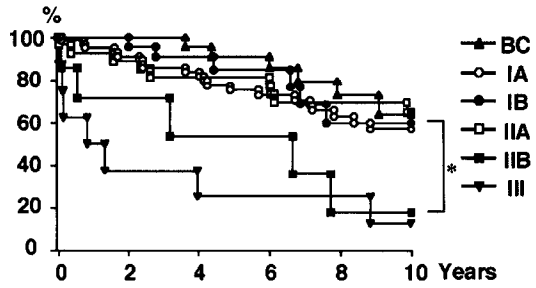

Fig. 1 Percentage of graft survival (up to 10 years) of study patients allocated to each Banff category (taking the worst biopsy for each patient). *Borderline change (*BC*) vs IIB, $P<0.01$; IA vs IIB, $P<0.05$; IB vs IIB, $P<0.05$; IIA vs IIB, $P<0.05$; BC vs III, $P<0.0001$; IA vs BC, $P<0.001$; IB vs III, $P<0.01$; IIA vs III, $P<0.01$; log-rank analysis

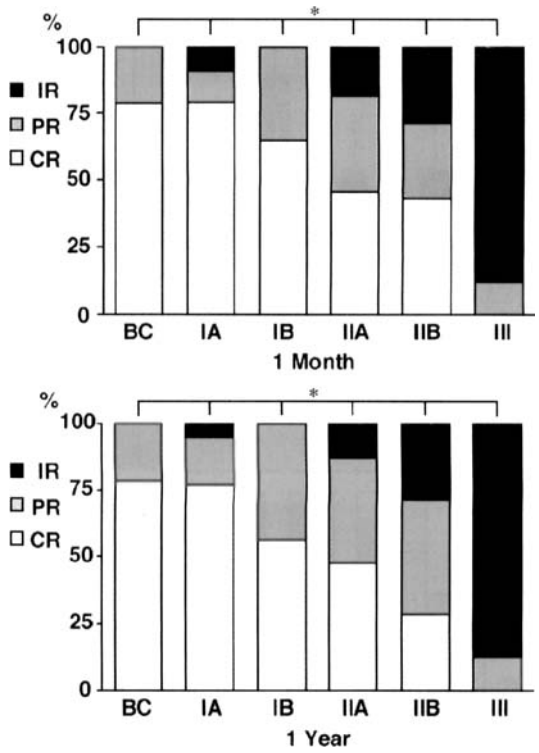

Fig. 2 Proportional bar chart showing the association of Banff grading (taking the worst grade for each of the categories at 1 month and 1 year after acute rejection episodes) and effect of anti-rejection therapy (*BC* borderline change, *CR* complete recovery from rejection, *PR* partial recovery from rejection, *IR* irreversible rejection). *$P<0.0001$, χ^2-test

type IA, and IB rejection showed complete or partial reversal, whereas in the case of type III rejection 87.5% of the patients were classified as being in the IR category at both 1 month and 1 year after rejection episodes.

Correlation with clinical follow-up data

Changes in graft function after rejection treatment correlated with histological grade of acute rejection at 1 and 2 years after transplantation (Fig. 3). There was no statistical difference in required antihypertensive medication among the different Banff 97 gradings. Proteinuria was not affected by the severity of acute rejection at a statistically significant level.

Recurrence of rejection episodes

The recurrence rate of rejection episodes was increased according to the histological grade of acute rejection, except for type III rejection (Fig. 4).

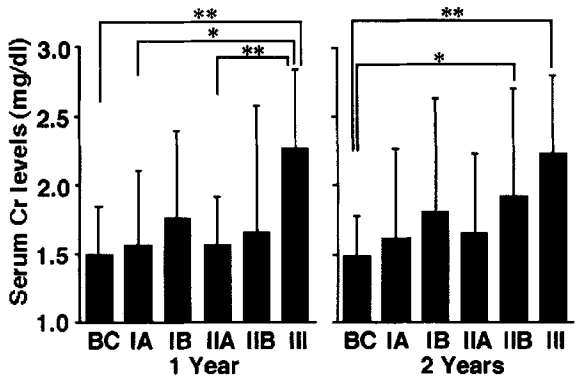

Fig. 3 Serum creatinine levels at 1 and 2 years after transplantation (*BC* borderline change). $*P<0.05$, $**P<0.01$, one-way ANOVA

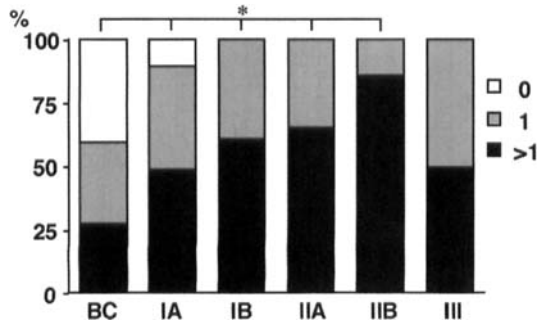

Fig. 4 Proportional bar chart showing the association of Banff 97 grading (taking the worst grade for each of the categories after transplantation), as diagnosed by retrospective review, and no rejection (0), single rejection (1), and multiple rejection episodes (> 1) (*BC* borderline change). $*P<0.001$, χ^2-test

Recovery of renal function according to histological scores

Figure 5 shows recovery from rejection correlated with pathological scores at 1 month and 1 year after acute rejection episodes. Glomerular, interstitial, and vascular scores were significantly lower for completely reversed rejections compared to the scores for partial or irreversible rejections.

Discussion

Kidney transplant recipients with acute rejection are at an increased risk of graft loss, mainly due to the development of chronic rejection [9]. Time of onset of acute rejection, number of rejection episodes, histological type, and reversal of rejection by immunosuppressive therapy are important determinants of graft survival. The Banff schema, a more detailed classification than those previously available, is a reproducible method for the grading of rejection which allows reliable semiquantitative evaluation of renal allograft histopathology [10]. The Banff 97 classification was developed using the Banff schema and the CCTT modification for diagnosis of renal allograft pathology at the fourth Banff conference. In this new classification, the presence or absence particularly of intimal arteritis was thought to be fundamental. The presence of intimal arteritis was closely correlated with adverse clinical outcome compared to the purely interstitial type of rejection [11, 12, 13]. Nickeleit et al. and Sibley et al. were able to demonstrate

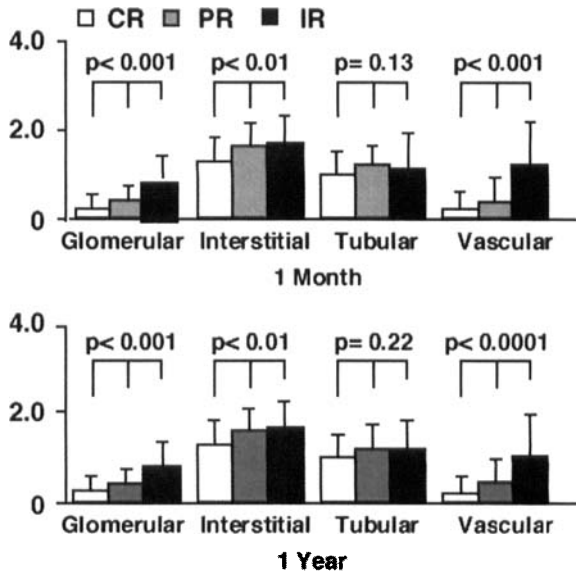

Fig. 5 Histological and quantitative criteria of acute rejection and reversibility of anti-rejection therapy at 1 month and 1 year after acute rejection episodes (*CR* complete recovery from rejection, *PR* partial recovery from rejection, *IR* irreversible rejection)

that grafts had a poorer prognosis if fibrinoid arterial necrosis was present [12, 14].

We examined whether the Banff 97 classification and scoring system accurately differentiated clinically relevant grades of rejection and whether the clinical outcome of rejection episodes correlated with the histological grade in a retrospective single-center study. A recent multi-center study cast severe doubt on the reproducibility of the Banff score since inter-observer variation was greater than previously reported [15]. It showed that great caution must be exercised when comparing biopsy results between institutions. There is evidence that some of this variation is genuine, particularly where the patient population is of different ethnic origin, but it seems very likely that part of this variation can be explained by discrepancies in grading criteria between different pathologists [15]. In the case of our single-center study, the pathologists at our institution have diagnosed the grade of acute rejection assiduously for many years so that there may be little inter-observer variation in our diagnoses.

Graft survival rate

The prognosis for vascular rejection was worse than that for cellular rejection. We found that the presence of acute vascular rejection of type IIB or III, as defined by severe intimal arteritis, was predictive of an increased likelihood of graft loss compared with BC, type IA, IB, and IIA acute rejection. Our findings suggest that there are significant differences in renal transplant pathology between type IIA (cases with mild-to-moderate intimal arteritis) and type IIB rejection (cases with severe intimal arteritis) with regard to graft survival.

Recovery of graft function

In our study, morphological changes and Banff 97 grading correlated statistically with recovery of graft function at 1 month and 1 year after rejection episodes. Figure 5 indicates that among the specific pathological lesions intimal arteritis is the most significant predictor of recovery from acute rejection at 1 year after rejection episodes. Our results indicate that the Banff 97 classification and scoring system provide clinically useful information guiding anti-rejection therapy and predicting rejection outcome.

Recurrent rejection episodes

The present study showed recurrence of rejection episodes to increase with histological grade, except in the case of type III rejection. Similar conclusions were presented by other studies that analyzed graft survival in recipients with no rejection compared with those with single or multiple rejections [9, 16, 17]. Recurrence of acute rejection was the most important covariant predictive of graft loss in a multivariate analysis of 665 primary cadaveric kidney transplants. Recipients with more than one episode of acute rejection showed a 7.5-fold increase in their relative risk of graft loss compared with those with no rejection [18]. We assume that because type III rejection is so severe, almost all patients experience graft failure earlier than with other types of rejection. Thus, there was no statistical difference in the rate of repeated rejection for type III compared with other types of rejection.

Correlation with clinical follow-up data

The clinical utility of the Banff 93–95 schema arises from single centers, multicenter studies, and databases [5, 19, 20, 21, 22, 23]. Of note, the Efficacy Endpoint Conference, a database of 953 rejection episodes, showed that Banff 93–95 grading correlated with measured loss of renal function (e.g., grade I-serum creatinine 2.8 ± 0.2 mg/dl vs grade II-serum creatinine 3.5 ± 0.2 mg/dl vs grade III-serum creatinine 4.1 ± 0.3 mg/dl) [24]. We were able to confirm that the Banff 97 classification also correlates with renal allograft function, especially with regard to severe vascular rejection (type IIB and III), where serum creatinine levels at 1 and 2 years after transplantation are significantly higher than those of other lower-grade rejections (Fig. 3).

In conclusion, our data confirm a significant association between histological grading for acute rejection according to the new, revised Banff 97 classification and graft outcome probability. We showed that morphological scores described in the Banff 97 scoring system are also appropriate parameters associated with reversibility of renal function. Among the specific pathological lesions, intimal arteritis was the most significant predictor of poor outcome.

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