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Correlation between Banff classification, acute renal rejection scores and reversal of rejection

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Correlation between Banff classification, acute renal rejection scores and reversal of rejection. The Banff classification of acute rejection is based on histologic grades and scores for borderline changes, glomerular, vascular, interstitial and tubular lesions. We reviewed 56 episodes of acute rejection occurring in 44 kidney allograft recipients (30 cadaveric and 14 living donor transplants), comparing Banff classification to degree of reversibility of rejection. Rejection reversal was defined as complete if serum creatinine returned $\leq 25\%$ of baseline, partial if creatinine was $> 25\%$ to $< 75\%$ of baseline, and irreversible if creatinine was $\geq 75\%$ of baseline or graft loss occurred. Eight biopsies were classified as borderline (SUM score 1.6 ± 0.5), 14 grade I (SUM score 3.3 ± 0.4), 19 grade II (SUM score 4.2 ± 0.3), and 15 grade III (SUM score 8.5 ± 0.4). SUM distinguished borderline and grade III rejections, but not grades I and II. Clinically, grade and SUM score correlated with rejection reversal. Complete reversal of rejection occurred in 93% of patients with grade I rejection, while 47% of patients with grade III had irreversible rejection. The mean SUM for complete reversal was 3.9 ± 0.34 and was different from SUM of partial (6.0 ± 0.86) and irreversible (8.5 ± 0.93), $P < 0.006$. Meanwhile, vascular scores were similar for rejections with complete (0.9 ± 0.2) or partial (1.0 ± 0.4) reversal, but significantly higher in those with irreversible rejection (3.0 ± 0.4, $P < 0.000$). Likewise, mean scores for tubulitis and interstitial inflammation were significantly higher for irreversible rejection. Resolution of rejection by steroids was correlated to low vascular score (steroid sensitive 0.65 ± 0.25 vs. steroid resistant 1.42 ± 0.18, $P < 0.01$), and low SUM score (steroid sensitive 3.7 ± 0.5 vs. steroid resistant 5.22 ± 0.43, $P < 0.04$). Neither scores for tubulitis nor interstitial cellular inflammation were predictive of steroid sensitivity. These data demonstrate that Banff scoring has clinical relevance in predicting rejection reversal and has implications to first-line therapy of rejection episodes.

Renal biopsies play a critical role in the management of transplant recipients. In recent years the value of renal allograft biopsies to recipient care has been emphasized by the widespread use of nephrotoxic immunosuppressants and other agents that compound the difficulty in establishing the clinical diagnosis of renal dysfunction episodes [1–4]. Such difficulty has been documented in studies demonstrating the wide variation between clinical impressions and the histopathologic findings on examination of renal tissue [5]. Yet despite their pivotal diagnostic role, the utility of allograft biopsies in predicting rejection outcome has been limited to reports correlating hemorrhagic and necrotizing lesions to graft failure and to those reports relating outcome to vascular involvement in rejection [5–7]. This may be in part secondary to the subjective grading of histological lesions of rejection and evaluation of the relative extent of injury of the renal compartments targeted by rejection. Besides hindering the predictive ability of allograft biopsies, the lack of standardization of biopsy interpretation has made comparisons of rejection incidence and treatment results between centers difficult. In addition, the subjective nature of biopsy interpretation has become a major problem in the design and analysis of multicenter transplant studies aimed at developing new immunosuppressive agents and immunosuppressive strategies.

Recognizing these problems, an international group composed of physicians working in different fields of transplantation generated the "Banff Working Schema" for the standardization of allograft biopsy interpretation [8]. The schema outlines histologic criteria to grade rejection. Moreover, it provides an objective semiquantitative estimation of the severity of renal injury. The histologic lesions in the glomeruli, tubules, interstitium, and blood vessels are graded on a scale of 0 to 3, then added to derive a numerical score for rejection. The "Banff Working Classification" provides a unique opportunity to explore the use of histologic parameters of graft injury to guide anti-rejection treatment in a prospective design based on the extent of morphologic evidence of renal injury. Prospective protocols may reduce unnecessary over or under immunosuppression, resulting in improved cost control, graft survival, and ultimately patient care.

The "Banff Working Classification" was utilized in a group of patients with renal allograft rejection. The aim was to examine whether the classification accurately differentiates clinically relevant grades of rejection. In addition, the clinical outcome of these rejection episodes was correlated to the pathological grading and scoring of the biopsies. This attempt represents one of the earliest efforts to validate the new classification in clinical practice [9, 10].

Methods

Biopsy procedure and analysis

Between January 1992 and October 1994 kidney allograft biopsies examined in the Pathology laboratory of the University of Tennessee-Memphis and diagnosed with rejection have been evaluated according to the Banff Working Classification. An

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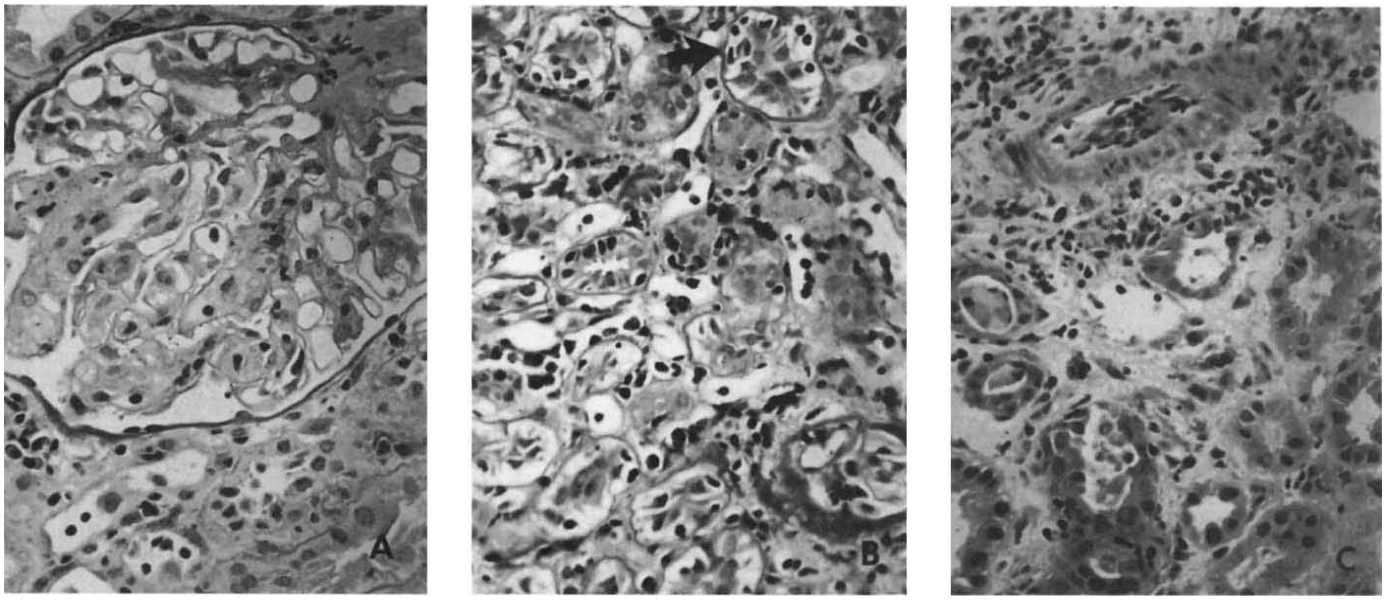

Fig. 1. *Histopathologic features of acute renal allograft rejection (original magnification ×400)* **(A).** Acute glomerulitis characterized by endothelial swelling and margination of circulating leukocytes within the glomerular capillaries (PAS). **(B)** Acute tubulitis of moderate grade (t2), a cross section of renal tubules is infiltrated by 7 mononuclear cells (arrow), there is also diffuse interstitial inflammation (PAS). **(C)** Intimal arteritis with endothelial proliferation and invasion of the intima by mononuclear inflammatory cells causing compromise of the arterial lumen (H&E).

adequate number of glomeruli (> 7) was required for inclusion in the biopsy review. For this report, cases with rejection were excluded if any of the following conditions existed: recipient's age less than 18 years, evidence of chronic allograft nephropathy defined by the presence of interstitial fibrosis and tubular atrophy, with or without intimal arterial thickening, in greater than 20% of the biopsy surface area, rejection episodes precipitated by treatment noncompliance, or when anti-rejection treatment was initiated prior to the biopsy. Allograft biopsies were performed with ultrasound guidance, using the automatic spring-loaded core biopsy system. Tissue samples were immediately divided, and one part was fixed in Carson's fixative for paraffin embedding, using standard processing techniques for light microscopy. A second part of the biopsy was snap frozen in liquid nitrogen for immunohistochemical studies, if needed. Serial 2 μm thin sections were cut, and several sets, each composed of three slides, were stained with hematoxylin and eosin, Periodic acid-Schiff, and Methenamine-silver, using standard staining techniques.

The slides were reviewed to grade the acute rejection and to assign a numerical score for the different pathologic components, according to the guidelines of the Banff Working Classification. Briefly, four grades of rejection were described: very mild rejection (borderline) includes cases with mild interstitial inflammation and mild tubulitis; Grade I (mild rejection) is a cellular rejection with interstitial infiltrate in more than 25% of the biopsy and with moderate tubulitis; Grade II (moderate rejection) has a significant interstitial inflammation, severe tubulitis and/or mild or moderate intimal arteritis; Grade III (severe rejection) includes severe intimal arteritis or evidence of focal infarction or interstitial hemorrhage. The morphologic changes in the glomeruli (g), interstitium (i), tubules (t) and arteries (v) (Fig. 1) were scored semiquantitatively from 0 to 3 (Table 1). Numerical scores were obtained after evaluation of series of levels on the biopsies. The SUM score for acute rejection was the sum of scores for $g + i + t + v$.

Immunosuppression and anti-rejection treatment

A quadruple, sequential immunosuppressive protocol utilizing high-dose steroids, azathioprine, OKT3 or ATGAM, and cyclosporine was used for all cadaveric recipients. Methylprednisolone (500 mg), azathioprine (5 mg/kg), and OKT3 (5 ml) or ATGAM (1 g) were administered as the patient was anesthetized for transplantation [11]. Methylprednisolone was decreased to 250 mg on the first postoperative day and to 125 mg on the second postoperative day and prednisone was initiated on the third postoperative day at a daily dose of 0.5 mg/kg and tapered to 0.2 mg/kg daily at three months post-transplant. Azathioprine was also given daily at a dose of 2 mg/kg. Cyclosporine, initiated in all patients by the third to seventh postoperative day, was begun at a daily dose of 4 to 8 mg/kg and adjusted to maintain a whole blood trough level of approximately 250 ng/ml (TDX whole blood monoclonal). Anti-lymphocyte therapy was continued for seven to ten days post-transplant. Prophylactic therapy for cytomegalovirus included acyclovir (200 mg) orally three times daily for six weeks, and fungal prophylaxis was accomplished with nystatin or oral ketoconazole. Ketoconazole was continued indefinitely in some patients in order to reduce the dose of cyclosporine necessary to maintain therapeutic cyclosporine levels. Identical triple immunosuppression without anti-lymphocyte induction was used in recipients of live donor allografts except when the recipient was highly sensitized, in which case quadruple therapy was used.

Renal allograft biopsies were performed when there was an acute rise in the serum creatinine of $\geq$ 0.3 mg/dl, in the absence of pre- or post-renal causes of graft dysfunction. Recipients with

Table 1. Semiquantitative scoring for acute renal allograft rejection according to the Banff Classification

	Numeric score	Description
Glomerular (*g*)	0, 1, 2, 3	no, mild, moderate, severe glomerulitis (*g* 3 = mononuclear cells in capillaries of all or nearly all glomeruli with endothelial enlargment and luminal occlusion)
Interstitial (*i*)	0, 1, 2, 3	no, mild, moderate, severe interstitial mononuclear and lymphocytic cell infiltration (*i* 3 = ≥50% of parenchyma is inflamed)
Tubular (*t*)	0, 1, 2, 3	no, mild, moderate, severe tubulitis (*t* 3 = >10 mononuclear cell per tubule or per 10 tubular cells in several tubules)
Vascular (*v*)	0, 1, 2, 3	no, mild, moderate, severe intimal arteritis (*v* 3 = severe intimal arteritis and/or transmural arteritis and/or hemorrhage and recent infarction)

Adapted from: Banff working classification of kidney transplant pathology. *Kidney Int* 44:411–422, 1993.

delayed graft function had routine biopsies on days 7 and 14 post-transplantation, then weekly for the duration of dysfunction. Treatment of histologically-proven acute rejection was based on a protocol which called for initial high-dose steroid pulses (10 mg/kg of methylprednisolone, maximum 500 mg/day) on three successive days. Response to steroid treatment was defined as a drop in serum creatinine of ≥ 0.3 mg/dl on a minimum of two successive days accompanied by a doubling of urine output. For steroid resistant rejections anti-lymphocyte therapy was instituted with either OKT3 or ATGAM. OKT3 was given for 10 days at 5 mg/day i.v., and patients were monitored during therapy by measurement of OKT3 serum levels and percent peripheral CD3 positive cells. ATGAM was used in patients with anti-OKT3 antibodies and was given at a dose of 1 g/i.v. for ten days. ATGAM dosage was adjusted based on percent peripheral CD2 positive T-lymphocytes.

Patients and clinical follow-up data

Clinical data, collected from the data base system of the transplant service at the University of Tennessee (Transplant Information Network, Medical Services Research Group, Inc., Memphis, TN, USA) included recipient demographics, data related to the clinical profile of the recipients at the time of rejection, and the response to anti-rejection treatment. Recipient demographics included age, sex, race, pre-transplant sensitization as measured by reactivity to a panel of lymphocytes (PRA), and number of HLA antigens matched to the donor. In addition, the transplant type (living vs. cadaveric), transplant number, days to onset of rejection from transplantation and whether post-transplant delayed graft function (DGF) existed at the time of rejection diagnosis were recorded. The degree of reversibility of the rejection was determined by comparing the serum creatinine level measured two weeks after completion of anti-rejection treatment (post-treatment creatinine) to the stable baseline serum creatinine prior to the rejection episode (pre-rejection creatinine). To be considered a complete reversal of rejection, a return of post-treatment creatinine to within 125% of the pre-treatment level was required. In patients with post-transplant DGF, complete reversal of rejection was defined as biopsy-proven resolution of rejection or resumption of renal function and achievement of a normal serum creatinine. A partial resolution of rejection was defined as a post-treatment creatinine improvement following anti-rejection treatment but only achieving 126 to 175% of the pre-treatment baseline serum creatinine. In patients with DGF, partial resolution of rejection was defined as recovery of renal function with a decline in serum creatinine but failure to reach normal levels or as the persistence of milder rejection on repeat biopsy. Rejection was considered to be irreversible if the post-treatment creatinine was more than 175% of the pre-treatment serum creatinine or if loss of graft function occurred. Non-resolution of rejection changes on follow-up biopsies for persistent DGF was also considered irreversible rejection.

Statistical analysis

Comparisons were made between the grades and scores for acute rejection and the previously defined parameters of steroid sensitivity and reversibility. Statistical analysis was performed using a microcomputer software program, JMP® Version 2.0.5 Software for Statistical Visualization on the Apple® Macintosh® (SAS Institute Inc., Cary, NC, USA). One-way analysis of variance was used to determine the difference between groups as means comparisons. Student's *t*-test was used to evaluate differences between individual groups. Chi-square was used to compare categorical data. Results were considered to be of statistical significance for P values < 0.05.

Results

The fifty-six rejection episodes in the study occurred in 44 patients, with 12 recipients having more than one rejection episode. The cohort of recipients included 21 African Americans and 23 Caucasians; 30 (68%) were males; age ranged from 18 to 68 years (mean 40 years); the mean peak PRA was 17 ± 5% (range, 0 to 95). Twenty-six (59%) of the 44 kidney allografts were procured from a cadaveric source and thirteen (30%) from a living related donor. Four were combined kidney-pancreas cadaveric allografts, and one was from a live unrelated donor. The mean HLA antigen match was 2 with a range of 0 to 4 antigens matched. The average cold ischemia time for cadaveric kidneys was 23.0 ± 1.5 hours, and two patients had received a previous kidney transplant. Rejection occurred a mean of 167 ± 43 days after transplantation (range, 5 to 1710 days, median 41 days). The average percent rise in serum creatinine from baseline was 37 ± 3% (mean ± SEM) at the time of biopsy. At the time of rejection diagnosis, the mean cyclosporine A (CsA) level was 199 ± 15 ng/dl, and patients were receiving an average of 105 ± 5 mg/day of azathioprine and 25 ± 2 mg/day of prednisone. One patient was not receiving steroids, four were in the process of being withdrawn from steroids, and three were not receiving Imuran. Three patients had low (<25 ng/dl) CsA levels, two had not started CsA, and one had severe diarrhea resulting in decreased CsA absorption.

Pathological scoring

Of the 56 biopsies examined, 8 were classified as demonstrating borderline changes, 14 had mild rejection (Grade I), 19 had moderate rejection (Grade II), and 15 had severe rejection (Grade III). Table 2 outlines the Banff numerical scoring for the biopsies according to the pathologic grade of rejection. The mean

Table 2. Banff numerical scoring for all biopsies reported according to grade

Grade	N	SUM	Glomeruli	Interstitial	Tubular	Vascular
Borderline	8	1.6 ± 0.5	0.13 ± 0.28	1.00 ± 0.30	0.38 ± 0.31	0.13 ± 0.21
I (Mild)	14	3.3 ± 0.4[d]	0.21 ± 0.22	2.07 ± 0.22	0.93 ± 0.24	0.07 ± 0.16
II (Moderate)	19	4.2 ± 0.3[d]	0.21 ± 0.19	1.68 ± 0.19	1.05 ± 0.20	1.26 ± 0.14[e]
III (Severe)	15	8.2 ± 0.4[a]	1.20 ± 0.21[b]	2.53 ± 0.22[c]	1.93 ± 0.22[c]	2.53 ± 0.17[a]

Shaded areas exhibit no statistical significance.
[a] $P < 0.0001$
[b] $P < 0.05$
[c] $P < 0.004$, Kruskal-Wallis analysis of variance
[d] $P < 0.05$, different from Borderline
[e] $P < 0.0000$, different from Borderline, Grade I and Grade III, Tukey-Kramer HSD

Table 3. Correlation between histologic grading of rejection and outcome

Rejection reversibility	B Borderline	I Mild	II Moderate	III Severe	Total
Complete	8	13	15	7	43[a]
Partial	0	1	4	2	7
Irreversible	0	0	0	6[b]	6
Total	8	14	19	15	56

[a] $P = 0.0011$, chi square
[b] Includes three graft losses

SUM score increased from borderline to Grade I to Grade II to Grade III. Biopsies with mild (Grade I) and moderate (Grade II) rejection were significantly different from those with borderline and severe rejection (Grade III). Additionally, vascular and glomerular scores were significantly higher in severe rejections (Grade III) compared to other grades.

Clinical pathologic correlation

Based on the reversibility criteria described previously, 43 (77%) rejection episodes were completely reversed, while seven (13%) had a partial reversal, and six (11%) episodes were classified as irreversible with three graft losses. Histologic grading of rejection correlated with rejection reversal ($P < 0.001$, Table 3). Complete reversal of rejection occurred in all episodes of rejection classified as borderline, in 93% of patients with Grade I rejection, and in 79% of Grade II rejections. However, only 47% of Grade III rejections were completely reversed while 40% were irreversible (Fig. 2). Reversibility of rejection correlated with the SUM scores. Complete rejection reversal was associated with significantly lower SUM scores (3.03 ± 0.34) than seen in episodes with partial (6.0 ± 0.86) or irreversible (8.50 ± 0.93) rejection (Table 4).

To further establish which of the morphologic features of rejection correlated with reversibility, we analyzed the relationship between the score of each morphologic component and clinical outcome (Table 4). Glomerular scores were not different for Irreversible rejection and Complete Reversal of rejection (0.83 ± 0.38 vs. 0.40 ± 0.14, respectively, $P = 0.5254$). In contrast, mean vascular scores were significantly higher (3.00 ± 0.40 vs. 0.91 ± 0.15, $P < 0.0000$) for irreversible rejections compared to those with complete reversal.

Steroid therapy alone completely reversed rejection in 46% of

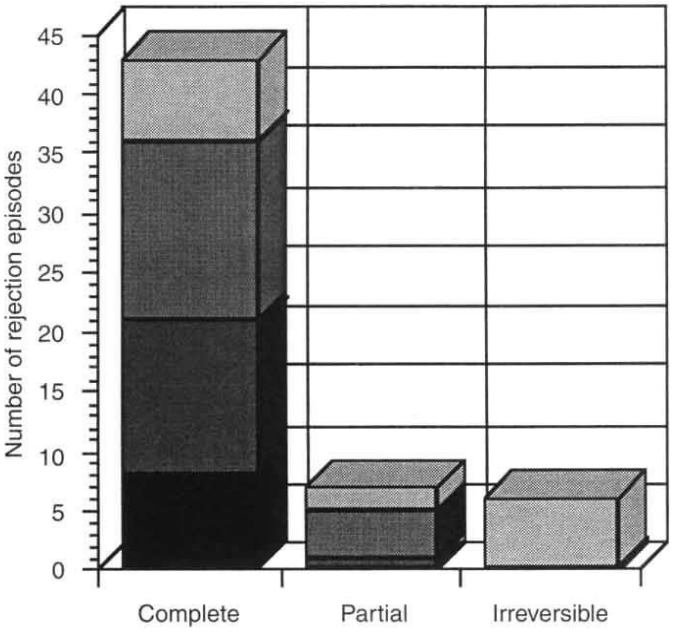

Fig. 2. *Relationship between histologic grading of rejection and rejection reversal.* Symbols are: (▨) Grade III, (■) Grade II; (■) Grade I; (■) Borderline.

all rejections graded as borderline, Grade I, or Grade II; and reversed only one (17%) Grade III rejection episode (Fig. 3). The remaining Grade III ($N = 14$) rejections required the addition of anti-lymphocyte antibody therapy. Thus, steroid therapy alone was successful in completely reversing rejection in only 36% of all episodes in this study. Glomerular scores were somewhat higher in patients who did not respond to steroids (0.64 ± 0.15 vs. 0.15 ± 0.20, $P = 0.054$; Table 5), while interstitial and tubular scores were not significantly different between steroid sensitive and steroid resistant rejections. However, the vascular scores were more than doubled in steroid non-responders versus responders ($P = 0.016$), and the total SUM score was significantly higher in steroid non-responders (mean SUM of responders = 3.7 ± 0.6 vs. 5.22 ± 0.43 in non-responders $P < 0.4$). Of the 36 rejection episodes determined to be unresponsive to steroid therapy, 31 (86%) were successfully treated with anti-lymphocyte antibody therapy. The rejection episodes that failed anti-lymphocyte therapy were two

Table 4. Relationship between pathological scoring of rejection and outcome

Reversibility	*N*	SUM	Glomeruli	Interstitial	Tubular	Vascular
Complete	43	3.93 ± 0.34	0.40 ± 0.14	1.72 ± 0.14	0.91 ± 0.14	0.91 ± 0.15
Partial	7	6.00 ± 0.86[d]	0.57 ± 0.35	2.57 ± 0.34[d]	1.86 ± 0.34[f]	1.00 ± 0.37
Irreversible	6	8.50 ± 0.93[aef]	0.83 ± 0.38	2.50 ± 0.37[b]	2.17 ± 0.37[ce]	3.00 ± 0.40[ag]

[a] $P = 0.0006$
[b] $P < 0.02$
[c] $P < 0.007$, Kruskal-Wallis analysis of variance
[d] $P < 0.05$, different from Complete
[e] $P < 0.01$ different from Complete
[f] $P < 0.05$ different from Partial
[g] $P < 0.0000$ different from Complete and Partial, Tukey-Kramer HSD

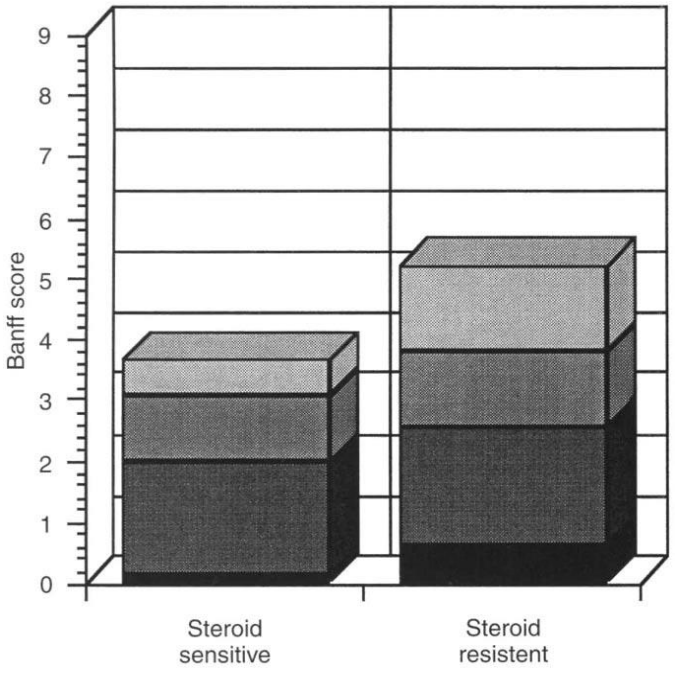

Fig. 3. *Relationship between pathological scoring and reversibility of rejection by steroids alone.* Symbols are: (□) vascular; (▩) tubular; (■) interstitial; (■) glomeruli.

Grade II and three Grade III rejections. Interestingly, there was a significantly higher tubular score for these anti-lymphocyte non-responders (1.00 ± 0.16 for anti-lymphocyte responders vs. 2.2 ± 0.4 for non-responders, $P = 0.0094$).

Discussion

This report summarizes an attempt to test the usefulness of the Banff Working Classification in clinical practice. The data demonstrate that the Banff classification and scoring system differentiates clinically relevant grades of rejection, and that the total SUM score of acute rejection and the vascular score are the strongest correlates to rejection reversibility. Acute tubulointerstitial rejections with a SUM score less than 4 are most likely reversible and steroid responsive, while most vascular rejections are steroid resistant. A SUM score equal to or greater than 6 is associated with an increased likelihood of steroid resistance or irreversibility of the rejection. Conventional anti-rejection treatment (steroids and antilymphocyte agents) failure occurred in greater than one-half of Grade III acute rejection and in those rejections with a vascular score of 3. These results indicate that using the Banff schema allows for objective semiquantitation of the histological lesions and provides clinically useful information to guide anti-rejection therapy and predict rejection outcome.

Prior to the introduction of the Banff Schema, there were several attempts to devise an acute rejection index [12, 13]. Finkelstein et al [12] based their index on semi-quantitative analysis of nine histologic features summing rejection changes and their effect on graft structure. They defined scoring levels that were indicative of acute rejection and demonstrated that response to therapy was predicted by histology. Prediction of response to anti-rejection treatment was, however, subjectively based on the pathologist's overall impression. Similarly, Parfrey et al [5] proposed morphologic, clinical, and combined clinical and morphologic indices to predict rejection outcome. The morphologic index devised by Parfrey had a negative predictive value, that is, histologic features of graft injury were a better predictor of return to dialysis than clinical parameters of renal function during rejection. The combination of both clinical and morphologic data improved the prediction of graft outcome. In the Banff Schema, the summation scores of tubular, interstitial, and vascular lesions are equivalent to the previously reported acute rejection index. Scoring in the Banff Schema is more detailed, encompassing all possible morphologic variables and grades. Moreover, more specific guidelines have been described for scoring by the Banff criteria, making it more objective and easier to apply than previously-described rejection indices. In addition, a recent report has demonstrated the schema to be reproducible among the study Banff group pathologists [9].

The relative importance of the severity and distribution of rejection pathology in the various renal compartments and their relation to rejection resolution is reflected in the semiquantitative scoring of the Banff Schema. Intimal arteritis and tubulitis are recognized as the principal indicators of acute rejection. The severity of infiltration of the renal tubules by mononuclear inflammatory cells, that is, tubulitis, differentiates tubulointerstitial rejection from mild inflammation characterized as borderline changes, while the presence of intimal arteritis upgrades acute rejection to either moderate or severe, regardless of the severity of the interstitial inflammation. Stressing vascular changes in rejection grading is based on studies that identified intimal arteritis as pathognomonic for acute rejection [15–17], and on evidence that the biological behavior of vascular rejection is quite different from that of pure cellular rejection [12, 13, 18]. It has been shown that the one-year graft survival for patients with

Table 5. Ability to reverse rejection by steroids alone

Reversal by steroids alone	SUM	Glomeruli	Interstitial	Tubular	Vascular
Yes, $N = 20$	3.70 ± 0.58	0.15 ± 0.20	1.85 ± 0.22	1.05 ± 0.23	0.65 ± 0.25
No, $N = 36$	5.22 ± 0.43[a]	0.64 ± 0.15	1.94 ± 0.16	1.22 ± 0.17	1.42 ± 0.18[b]

[a] $P = 0.0408$
[b] $P = 0.0155$, ANOVA

vascular rejection is significantly lower than in those with predominantly cellular inflammation and that severe vascular changes are consistent predictors for graft failure [19, 20]. Furthermore, the presence of vascular changes affects the rate of rejection reversal, even in the context of newer, more potent anti-rejection therapies [21–23].

Tubulitis is a reliable indicator of tubulointerstitial rejection, but its impact on functional recovery of the allograft has not been adequately studied. The presence of severe tubular necrosis enhanced the negative predictability of vascular pathology during the course of acute rejection [5]. Recent evidence suggests that renal tubules are not equally involved by cellular rejection and that both the distal convoluted tubules and the collecting ducts are more vulnerable to invasion by T-lymphocytes [22]. The Banff schema accommodates this segmental variation in tubular inflammation during rejection, as the severity of tubulitis is determined by the number of invading inflammatory mononuclear cells in the most affected tubule. In the current study, the tubulitis scores appeared to parallel the increasing grade of rejection, with Grade III rejection demonstrating significantly higher tubulitis scores than other grades. Mild tubulitis was associated with complete rejection reversal, while severe tubulitis was significantly more pronounced in patients who failed anti-lymphocyte therapy.

Although scoring for glomerular inflammatory lesions has been incorporated into the Banff Schema, it was stated that the significance of the glomerulitis was not clear. Rejection glomerulitis is defined by endothelial swelling, intraglomerular margination of mononuclear cells, and glomerular thrombosis or necrosis [24, 25]. This pattern of allograft glomerulitis was initially described in recipients with cytomegalovirus (CMV) infection and, thus, was thought to be a CMV-associated glomerulopathy [26]. Now, it is widely accepted that acute allograft glomerulopathy is a distinctive form of transplant rejection, that may be modified or induced in some recipients by a CMV infection [27, 28]. Although slightly higher glomerular scores were found in steroid-resistant rejection and in Grade III rejections, acute allograft glomerulitis was not frequently found in our biopsies and did not statistically correlate with rejection outcome.

The application of the Banff Schema in clinical practice is not without problems. As with all new pathology-based criteria, uniform application and acceptance requires increased clinical experience and demonstration of validity in everyday clinical practice. To date, attempts at validating the utility of Banff Schema have yielded encouraging reproducibility of results. Although the initial Banff report did not suggest summing of the scores for various rejection histologies, this study as well as the body of literature have used SUM scores to differentiate rejection grades. Conceptually the use of SUM scores could be problematic by giving equal weight to rejection lesions of various significance and may complicate the ability to differentiate clinically relevant rejection grades. Routine use of Banff Schema in clinical practice has identified some areas of additional potential problems, particularly the overlap between mild and moderate rejection by SUM scores. This overlap is further compounded by the fact that SUM scores do not distinguish cellular rejection with a heavy cellular infiltrate from vascular rejection, although these two forms of rejection may have very different outcomes. This may be clinically important, particularly as it has been shown that pure cellular rejection, even with heavy interstitial inflammation, does not preclude functional recovery of the allograft and that interstitial inflammation is present in a prominent proportion of stable renal grafts without a detrimental impact on long-term function or survival [29–31]. For example, a SUM score of 5 can be obtained in biopsies with the following rejection features: (Example 1) c = 1, t = 2, v = 2; (Example 2) c = 2, t = 2, v = 1; (Example 3) c = 3, t = 2, v = 0. Because of the variations in rejection severity in the renal compartments, the biological behavior of these rejections (one predominantly vascular, Example 1; the other cellular, Example 3) is expected to be diverse [7] despite identical scoring on the Banff Schema. Therefore, at the present time, interpretation of the semi-quantitative results from Banff Schema should be done utilizing the collective information on grade, SUM score, and vascular score.

In conclusion, this study demonstrates that the histologic parameters of rejection graded according to the Banff Schema can be predictors of rejection outcome. A severe vascular rejection with a score of 3 and a SUM score of 6 or greater is likely to be steroid-resistant and more likely to have incomplete reversal, even with anti-lymphocyte therapy. On the other hand, the prognosis of a moderate tubulointerstitial rejection is dependent on the presence of associated vascular injury and the total score of rejection. Further work is needed to eliminate potential overlap in Banff grading and scoring and to further enhance the clinically utility of the schema.

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