Abstract. Diagnosis of allograft dysfunction relies on the assessment of arterial lesions. This study was designed to evaluate the prognostic significance of common specific vascular lesions in acute allograft rejection. Renal allograft biopsies (n = 111) with acute cellular rejection were scored for endarteritis, mononuclear cell adherence to endothelial cells, endothelial activation, fibrinoid necrosis, foam cells, and intimal fibrosis. These vascular lesions and other classic histologic features were correlated with outcome. Rejection with endarteritis (found in 54% of biopsies) was less responsive to steroid treatment than rejection without endarteritis, as judged by recovery of creatinine in 3 wk ($P = 0.03$). Larger numbers of sampled arteries improved the predictive accuracy. Sticking of mononuclear cells to endothelial cells also correlated with steroid resistance ($P < 0.05$). Rejection with or without endarteritis responded to OKT3/antithymocyte globulin treatment equally well (61% versus 65%, respectively). Rejection with fibrinoid arterial necrosis (4% of biopsies) did not respond to either steroids or antibodies (0%). One-year graft failure was 21% without endarteritis, 28% with endarteritis, and 100% with fibrinoid necrosis. Activated endothelial cells and interstitial hemorrhage were associated with endarteritis and graft failure (all $P < 0.05$). None of the other scored features had any statistically significant correlation with outcome. Thus, specific arterial lesions (endarteritis, fibrinoid necrosis, activated endothelial cells, mononuclear cell margination) and interstitial hemorrhage, but not the extent of the interstitial infiltrate or tubulitis, are correlated with response to antirejection therapy and/or 1-yr clinical outcome. Grading systems for therapeutic trials and clinical management should emphasize scoring of specific vascular lesions.

Rejection episodes are common after transplantation, particularly those classified as acute cellular rejection (ACR, or acute rejection). Because acute rejection responds variably to modern antirejection therapy and may presage longer-term outcome, characterization of this pathologic reaction has attracted some interest. Many articles have dealt with the histologic appearance of acute rejection, and several classification approaches have been proposed (1-3). However, detailed histologic data are needed to correlate the specific histologic findings in acute rejection with the response to therapy and clinical outcome, in order to refine and validate these classification schemes.

Most researchers regard vascular (arterial) lesions as key determinants of outcome. However, the term "vascular rejection" is often ambiguous, applied to all vascular lesions found during rejection ranging from thrombosis, fibrinoid vascular necrosis, and endarteritis to myointimal proliferation with fibrosis. Vascular rejection is commonly believed to have an ominous prognosis. However, it is unknown which one (or all) of the alterations mentioned above might be relevant to the deterioration of graft function. Other features are of uncertain significance, such as activated endothelial cells and sticking of mononuclear cells to the endothelium. Another important and disputed question is whether the extent of interstitial mononuclear inflammation or tubulitis is associated with the clinical severity of a rejection episode (2,3).

In this retrospective study, we reviewed distinct morphologic findings in acute rejection and correlated their presence with the response to antirejection treatment and graft function or survival 6 and 12 mo later. We placed special emphasis on endarteritis and other vascular lesions. The aim of our study was to determine whether any histologic feature carried specific prognostic or therapeutic significance.

Materials and Methods

Biopsy Samples

The study population consisted of patients who had renal allograft biopsies to evaluate the cause of graft dysfunction at the Massachusetts General Hospital, Boston, Massachusetts, or St. Vincent's Medical Center, Los Angeles, California, from 1990 to 1993. Histologic analysis was performed on those 111 biopsies that met the histologic criteria for acute rejection (see below). Those with a histologic diagnosis of glomerulonephritis, hyperacute rejection, thrombotic microangiopathy, chronic rejection, or evidence of predominant cyclo-
sporine/tacrolimus toxicity were excluded. The biopsies were taken 41 ± 38 d posttransplantation (range, 6 to 224) and included 80 initial biopsies, 27 second biopsies, three third biopsies, and one fourth biopsy, from a total of 79 patients.

**Diagnostic Criteria**

Acute rejection was defined by the Cooperative Clinical Trials in Transplantation (CCTT) classification (3). In brief, CCTT recognizes three types of acute rejection. In type I rejection (tubulointerstitial), a mononuclear inflammatory cell infiltrate occupies ≥5% of the renal cortex, and at least three tubules show tubulitis in 10 consecutive high-power fields from the most affected areas of interstitial inflammation (with one infiltrating mononuclear cell per tubular cross section being sufficient to represent tubulitis). In addition, at least two of the following three features were required: interstitial edema, activated lymphocytes, and acute tubular injury. Type II rejection has endarteritis with or without interstitial rejection. Endarteritis is defined as the presence of mononuclear inflammatory cells in the subendothelial space, thus having penetrated through the endothelial cell layer. Other features of vascular injury (such as myointimal hyperplasia and new intimal collagen accumulation, foam cells, fibrin deposition, fibrinoid vascular wall necrosis, etc.) are not included in the term endarteritis. Type III rejection has fibrinoid arterial necrosis or transmural inflammation.

**Review Process**

Needle biopsies fixed in formalin and stained with hematoxylin and eosin and/or periodic acid-Schiff were reviewed without knowledge of clinical data. A single section was marked for analysis, although adjacent sections were studied in equivocal cases (such as for confirmation of endarteritis). Coded slides were reviewed independently by at least two of the three renal pathologists (Drs. Nickebeit, Poletti, and Colvin). In those cases (<5%) with disparate findings (e.g., presence or absence of endarteritis), a consensus was reached by rereview with all three pathologists and used for subsequent analyses. When the result was numerical (e.g., the number of vessels), the scores were averaged.

**Histologic Features Scored**

The number of large and small arterial cross sections in the sample was recorded separately. The small arteries included arterioles and the prearterioles just before the final branching; these are collectively called “arterioles” in this article. The vascular lesions were scored as the number of vessels (arteries versus arterioles) with the particular feature, so that the percentage as well as the presence or absence of the feature could be calculated:

1. Mononuclear cells invading the subendothelial layer (endarteritis) (Figure 1).
2. Mononuclear cells sticking to the endothelium (without invading the subendothelial intimal layer) (Figure 2).
3. Activated endothelium (enlarged basophilic cytoplasm) (Figures 2 and 3).
4. Fibrinoid arterial necrosis (Figure 3).
5. Intimal foam cells (Figure 4).
6. Intimal fibrosis.
7. Mononuclear cell interstitial infiltrate in the cortex (percentage of involved area).
8. The number of tubular cross sections involved by tubulitis counted in 10 consecutive high-power (×40) fields in the area of most pronounced interstitial inflammation. According to standard criteria, tubulitis was defined as a single mononuclear cell invading a single nonatrophic tubule, thus having penetrated through the tubular basement membrane of normal thickness. No attempt was made to evaluate the severity/extent of tubulitis in a single tubular cross section.
10. Eosinophils (present/absent).
11. Interstitial hemorrhage (present/absent).

**Clinical Data Evaluated**

To correlate morphologic findings with outcome and response to treatment, the following clinical data were analyzed:

1. Baseline immunosuppressive therapy (cyclosporin A, corticosteroids, azathioprine, or other agents).
2. Treatment of rejection episode (pulse steroids, OKT3, antithymocyte globulin [ATG], or other). Unresponsiveness to bolus steroid therapy often led to subsequent rescue attempts with ATG or OKT3; thus, most patients under the latter regimen had also been treated with steroids.
3. Serum creatinine levels (prerejection baseline and peak levels during rejection episode 3 wk, 6 mo, and 12 mo after biopsy).
4. Transplant nephrectomy or return to dialysis.

The response to antirejection medication was judged by correlating serum creatinine levels 3 wk after biopsy with the prerejection baseline creatinine levels. A complete treatment response was defined as a serum creatinine level 3 wk after biopsy ≤110% of the baseline level. Graft failure was defined as transplant nephrectomy, return to dialysis, or a new baseline serum creatinine level of ≥5 mg/dl. One-year follow-up was available on 73 of 79 patients (103 of 111 biopsies). Overall, 20 grafts failed in the first year (18 dialysis/nephrectomy and two were functioning with a creatinine level >5 mg/dl).

**Statistical Analyses**

Associations between individual, categorically defined pathologic features (see above) and type of rejection, graft failure, and response to treatment were examined by analysis of contingency tables (using a two-tailed Fisher’s exact test for 2 × 2 tables or a χ² test for larger tables). Associations between individual, interval scale pathologic features and the aforementioned variables were examined by Kruskal-Wallis nonparametric ANOVA, or by parametric one-way ANOVA when the assumptions of a parametric analysis were satisfied. The latter methods were also used to examine the associations between creatinine levels and individual, categorically defined pathologic features. The BMDP Statistical Package (version 7.0, Dynamic, BMDP Co., Berkeley, CA) was used for analysis. The results are presented as mean ± SEM. Little or no difference in outcome was found between biopsies of initial and subsequent episodes; thus, all cases were combined, except where specifically noted.

**Results**

**Endarteritis**

Endarteritis (type II rejection) was present in 54% of biopsies when either all (60 of 111) or first biopsies (43 of 80) were considered (Table 1). Endarteritis could be detected along the entire length of the arterial vasculature (from arcuate arteries to arterioles). Among biopsies with endarteritis, 19.3 ± 9.7% of the arterial and arteriolar cross sections showed characteristic...
lesions. Endarteritis was more often found in larger arteries (27.4 ± 17.0% of cross sections) compared with the smaller branches (12.7 ± 11.1%).

The presence of endarteritis adversely influenced the response to bolus steroids (Table 1). Rejection was completely responsive to bolus steroids in only 19% of patients (8 of 42) with endarteritis; in contrast, 45% (13 of 29) of those without endarteritis fully responded to bolus steroid therapy (P = 0.03). When just the first biopsy was considered, 17% of those 35 evaluable patients with endarteritis responded to steroids, versus 50% of those 20 without endarteritis (P = 0.012). The fraction of arteries (or prearterioles/arterioles) with endarteritis did not correlate with the response to steroids. For example, of those 24 evaluable with >30% involved arteries, 17% responded, versus 22% of those 18 with ≤30% (NS).

The presence of endarteritis did not adversely affect the response to ATG or OKT3 (Table 1). The majority of those with endarteritis responded fully (61%; 23 of 38); similarly, 65% (13 of 20) of those without endarteritis responded fully to either OKT3 or ATG (NS). Specifically, 60% without endarteritis (9 of 15) and 60% with endarteritis (21 of 35) responded completely to OKT3; the corresponding response rate for ATG was 80% (4 of 5) and 67% (2 of 3), respectively. There was a trend in the group with endarteritis for the extent of the endarteritis to adversely affect the OKT3/ATG response. Of those 18 evaluable with >30% involved arteries, 41% responded completely, whereas 75% of those 20 with ≤30% responded (P = 0.057). No trend was evident in the smaller vessels (data not shown).

Graft failure at 1 yr was 28% in the presence of endarteritis compared with 21% in those without endarteritis, but this difference did not reach statistical significance. The trend in decreased renal function at 6 and 12 mo among those with endarteritis was not statistically significant (Table 1). To detect differences in the deterioration of graft function in a more sensitive manner, we also analyzed the delta changes between baseline, peak, 6-mo, and 12-mo creatinine levels, and no statistically significant differences were found. Cases with.

Figure 1. Endarteritis. (A) A small artery (arteriole or prearteriole) has a small cluster of mononuclear cells under the endothelium (arrow). This finding defines endarteritis. Biopsy was taken 9 d posttransplant; rejection episode did not respond to bolus steroids, but did respond to OKT3. Serum creatinine was 1.2 mg/dl 1 yr later. Hematoxylin and eosin (H&E) stain, ×560. (B) Another larger artery has mononuclear cells circumferentially under the endothelium; the media have no appreciable alteration. Biopsy was taken 32 d posttransplant; rejection episode did not respond to bolus steroids, but did respond to antithymocyte globulin. Serum creatinine was 3.0 mg/dl 1 yr later. Periodic acid-Schiff (PAS) stain, ×560.
Figure 2. Sticking of mononuclear cells. Two arterioles have mononuclear cells in contact with the luminal surface of the endothelium ("sticking"). This graft biopsied at day 32 had type I rejection and was lost to rejection within 6 wk. H&E stained section, ×438.

endarteritis did not show any differences in baseline or peak serum creatinine levels during the rejection episode (data not shown). There was no correlation between the percentage of arteries or arterioles with endarteritis and outcome at 6 or 12 mo (data not shown).

The diagnostic accuracy of detecting vascular lesions depends solely on the adequacy of the biopsy core, i.e., the number of sampled arteries. The average number of arteries in all samples was 4.2 ± 1.6; the number of arterioles/prearterioles was 7.9 ± 1.6. Those with endarteritis had twice the average number of arteries in the sample than those without endarteritis (5.3 ± 1.6 versus 2.7 ± 1.6), as expected, because the probability of detecting endarteritis is a direct function of the number of vessels sampled. The probability of detecting endarteritis among four arteries can be calculated to be 75% \((P = (1 - f)^4)\), where \(f\) is the observed probability of endarteritis in a single artery sample [measured as 27% here], and \(n\) is the number of arteries sampled. If steroid responsiveness is a characteristic of those cases without endarteritis (type I), one would expect that the frequency of steroid responsiveness in this group would increase as the number of sampled arteries increases. Indeed, among those with type I rejection, responsiveness to steroids increases progressively with the number of arteries sampled, to 75% of those with four or more arteries, as does the renal function at 1 yr (Table 2).

**Fibrinoid Necrosis**

Fibrinoid necrosis (type III rejection) was an infrequent finding (4%) (Table 1). Transmural necrosis could be detected in both large and small arteries/prearterioles. Most often, only segments of the vessel wall were necrotic. (In our series, the entire circumference was never totally involved.) All of the cases had activated endothelial cells, 75% had sticking of mononuclear cells, and 75% had endarteritis. Rejection episodes that displayed fibrinoid necrosis never responded fully to either steroids or antibodies (0%, 0 of 4). All patients fared poorly; 100% had graft failure within 12 mo of the biopsy \((P = 0.005\) versus types I and II combined).

**Other Vascular Lesions**

Enlarged (i.e., activated) endothelial cells with basophilic cytoplasm correlated with a poor 1-yr graft survival (44% versus 18%; \(P = 0.0041\) (Table 3). If the fibrinoid necrosis cases are excluded, the 1-yr graft failure rate is 38% \((P = 0.0255)\). The presence of activated endothelial cells was associated with resistance to OKT3/ATG treatment (33% responders versus 67% nonresponders; \(P < 0.001\)). There also was a correlation between activated endothelial cells and endarteritis. Activated endothelial cells were detected in 53% of cases with endarteritis versus 17% of biopsies without endarteritis \((P < 0.0001)\). Activated endothelial cells were found in all of the cases with fibrinoid necrosis.
An association was found between "sticking" of mononuclear cells and unresponsiveness to bolus steroid therapy ($P < 0.05$). The presence of mononuclear cells adherent to the endothelium often raises the suspicion of endarteritis. However, in this series, the correlation between sticking and endarteritis did not reach statistical significance (of those with sticking, 59% had endarteritis versus 50% of those without sticking). Graft failure at 12 mo was high among those with intimal fibrosis or foam cells. However, these associations did not reach statistical significance, probably because of the small size of these groups.

The intimal fibrosis in these samples was probably largely due to donor disease, because it was present in biopsies 6 to 71 d posttransplant. Foam cells in small arteries are usually regarded as a feature of chronic vascular rejection (versus donor arteriosclerosis). It was therefore notable that foam cells were seen as early as 15 d after transplantation (mean of 42 d; range, 15 to 106 d).

**Tubulointerstitial Lesions**

The presence of interstitial hemorrhage was associated with increased graft loss at 1 yr (14 of 34 versus 15 of 69; $P = 0.037$) (Table 3). Hemorrhage was more common in biopsies with endarteritis (40%) than in tubulointerstitial rejection (17%) ($P < 0.01$); all of the cases with fibrinoid necrosis had hemorrhage. No statistically significant correlations were found between deterioration of graft function and either the extent of cortical mononuclear cell infiltration or the frequency of tubulitis (Tables 4 and 5). Notably, no progressive trend is evident in outcome, in part because those with the sparsest infiltrate had a particularly poor prognosis. Neither the extent of the infiltrate nor the tubulitis correlated with the presence of endarteritis or fibrinoid necrosis. The presence of interstitial neutrophils or eosinophils had no obvious adverse effect on outcome.

**Discussion**

The histologic examination of a renal biopsy remains the gold standard in the evaluation of renal allograft dysfunction (1). Neither changes in serum creatinine levels nor techniques such as radionuclide scintigraphy or fine-needle aspiration give as reliable results as the evaluation of a standard needle core biopsy. Although previous studies have stressed the importance of certain vascular lesions, particularly fibrinoid necrosis and endarteritis, systematic correlations with outcome of these and the other specific lesions encountered in allografts are limited (reviewed in reference 1). This information would be of eminent interest to clinicians who ask for patient-specific prognostic information, and to those refining classification schemes of acute renal allograft rejection for clinical trials.

In the present study, distinct histologic features of acute cellular rejection were analyzed and correlated with response to therapy and 1-yr outcome. To determine whether any histologic change in the vasculature during acute rejection carries special significance, we placed emphasis on well defined arterial alterations. In particular, the importance of endarteritis was determined. Although endarteritis is a frequent finding in acute rejection (approximately 50% of cases), it has been dealt with in only a few previous reports (3–6) with small case numbers. Its clinical significance is still highly controversial. This is mainly because endarteritis is often not separated from cases with fibrinoid vascular necrosis, thrombosis, or even intimal proliferation (i.e., chronic features).

Endarteritis in the present study proved to be a marker for resistance to bolus steroid therapy. The sticking of mononuclear cells also correlated with steroid resistance. Perhaps most convincing of the association is that with a larger sample of arteries (to rule out endarteritis with greater reliability), the frequency of steroid responsiveness increases. The minimal adequacy requirement for CCTT classification is that two small arteries be present, a position that is well justified by our data. The outcome data from the present study are compatible with the CCTT report, which found that endarteritis increased the risk by sixfold of a clinically severe rejection (defined in part by steroid resistance) (3). Our observation that endarteritis fully responded to anti-T cell antibodies (ATG/OKT3) in more than 60% of rejection episodes is entirely consistent with the data reported previously with OKT3 (5) and supports the argument that endarteritis is T cell-mediated, or at least T
cell-deficient mice (7). Endarteritis in three earlier studies was associated with function and graft survival at 1 yr in patients with endarteritis, the demonstration of classic endarteritis in cardiac grafts in B cell-dependent. This hypothesis has received recent support by the major problem is its detection, endarteritis is very focal, acute tubulointerstitial rejection (60% statistically significant adverse prognostic feature compared with these four studies, endarteritis does emerge as a highly statistically significant adverse prognostic feature compared with acute tubulointerstitial rejection (60% versus 79% 1-yr graft survival; P < 0.01) (9).

Endarteritis was not an infrequent finding in our series and was noted in more than 50% of biopsies with acute rejection, a prevalence in agreement with previous reports (3–6). Despite the high prevalence of endarteritis, it is not clear that an attempt to grade the extent (i.e., severity) is warranted. Because endarteritis is very focal, the major problem is its detection, which is largely determined by the biopsy size. We found that in cases of acute rejection with endarteritis, only 27% of examined arterial cross sections showed characteristic lesions. Even if four arterial cross sections were present in a biopsy, the likelihood of finding endarteritis can be calculated to be only 7%. A grading scheme based on the number of affected arteries thus would not be practical. Grading based on the number of mononuclear cells in the subendothelial space and

<table>
<thead>
<tr>
<th>Type</th>
<th>Biopsies</th>
<th>Response To Antirejection Therapy</th>
<th>Serum Creatinine (mg/dl; mean ± SEM)</th>
<th>Graft Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n†</td>
<td>Bolus Steroids %b</td>
<td>6 mo</td>
</tr>
<tr>
<td>Tubulointerstitial (type I)</td>
<td>42</td>
<td>47</td>
<td>45 29 65 20</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>Endarteritis (type II)</td>
<td>54</td>
<td>60</td>
<td>19 42 61 38</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>Fibrinoid necrosis (type III)</td>
<td>4</td>
<td>4</td>
<td>0 4 0 3</td>
<td>6.7</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>111</td>
<td>28 75 62 61</td>
<td>2.5 ± 0.1</td>
</tr>
</tbody>
</table>

a Number evaluable.
b Percentage of complete response, defined as creatinine ≤110% of baseline 3 wk after biopsy.
c P = 0.03 versus type I (no endarteritis).

Table 2. The number of arteries sampled in cases of type I rejection correlates with accuracy of predicting steroid responsiveness

<table>
<thead>
<tr>
<th>No. of Arteries</th>
<th>Response to Bolus Steroids a % n</th>
<th>Creatinine (12 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>45 29</td>
<td>2.4 ± 1.6</td>
</tr>
<tr>
<td>≥2</td>
<td>50 24</td>
<td>2.3 ± 1.7</td>
</tr>
<tr>
<td>≥3</td>
<td>57 14</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td>≥4</td>
<td>75 8</td>
<td>1.9 ± 0.6</td>
</tr>
</tbody>
</table>

a For complete response, see Table 1.
Table 3. Other vascular and interstitial lesions versus outcome

<table>
<thead>
<tr>
<th>Lesion</th>
<th>% of Biopsies with Lesion</th>
<th>Steroid Response</th>
<th>Graft Failure at 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>reactive endothelium</td>
<td>40</td>
<td>22</td>
<td>33</td>
</tr>
<tr>
<td>sticking of mononuclear cells</td>
<td>68</td>
<td>21</td>
<td>44(^c)</td>
</tr>
<tr>
<td>intimal foam cells</td>
<td>8</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>intimal fibrosis</td>
<td>12</td>
<td>50</td>
<td>34</td>
</tr>
<tr>
<td>Interstitial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemorrhage</td>
<td>32</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>neutrophils</td>
<td>27</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>eosinophils</td>
<td>32</td>
<td>27</td>
<td>29</td>
</tr>
</tbody>
</table>

\(^a\) P values <0.05 indicated with footnotes. Presence or absence of lesion is given as a percentage.
\(^b\) P = 0.0041; if fibrinoid necrosis is omitted from analysis, P = 0.0255.
\(^c\) P = 0.047.
\(^d\) P = 0.037.

Table 4. Extent of interstitial infiltrate versus type of rejection and outcome

<table>
<thead>
<tr>
<th>Cortical Infiltrate (%)</th>
<th>Biopsies</th>
<th>Type of Rejection</th>
<th>Creatinine (12 mo)</th>
<th>Graft Failure at 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td>All (%)</td>
<td>Type I (%)</td>
</tr>
<tr>
<td>5 to 10</td>
<td>5 6</td>
<td>67 17 17</td>
<td>4.0 ± 1.4</td>
<td>50 50 4 0 1</td>
</tr>
<tr>
<td>11 to 25</td>
<td>12 13</td>
<td>54 46 0</td>
<td>1.9 ± 0.7</td>
<td>27 0 6 60 5</td>
</tr>
<tr>
<td>26 to 50</td>
<td>27 30</td>
<td>33 67 0</td>
<td>2.1 ± 0.4</td>
<td>18 13 8 20 20</td>
</tr>
<tr>
<td>51 to 75</td>
<td>28 31</td>
<td>48 48 3</td>
<td>3.0 ± 0.6</td>
<td>35 21 14 43 14</td>
</tr>
<tr>
<td>76 to 100</td>
<td>28 31</td>
<td>35 58 6</td>
<td>2.8 ± 0.5</td>
<td>29 30 10 22 18</td>
</tr>
</tbody>
</table>

\(^a\) Number evaluable.

Table 5. Extent of tubulitis versus type of rejection and outcome

<table>
<thead>
<tr>
<th>Tubulitis (tubules per 10 hpf)</th>
<th>Biopsies</th>
<th>Type of Rejection</th>
<th>Creatinine (12 mo)</th>
<th>Graft Failure at 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td>All (%)</td>
<td>Type I (%)</td>
</tr>
<tr>
<td>3 to 4</td>
<td>25 28</td>
<td>39 61 0</td>
<td>2.4 ± 0.4</td>
<td>32 46 11 24 17</td>
</tr>
<tr>
<td>5 to 6</td>
<td>43 48</td>
<td>40 54 6</td>
<td>2.7 ± 0.4</td>
<td>20 6 17 19 26</td>
</tr>
<tr>
<td>7 to 8</td>
<td>23 26</td>
<td>42 58 0</td>
<td>2.6 ± 0.6</td>
<td>38 13 8 54 13</td>
</tr>
<tr>
<td>&gt;8</td>
<td>8 9</td>
<td>67 22 11</td>
<td>3.5 ± 1.2</td>
<td>38 33 6 0 1</td>
</tr>
</tbody>
</table>

\(^a\) hpf, high-power field.
\(^b\) Number evaluable.

the grading of acute rejection based on the extent of the infiltrate or tubulitis (19,20).

Standardized protocols for the histologic typing (grading) of acute renal allograft rejection episodes are crucial for the analysis of therapeutic trials. These protocols have to be simple, reproducible, and relevant for prognosis and treatment. We provide further evidence that a simple typing of acute rejection, as proposed by the CCTT protocol (3), is clinically relevant. It seems appropriate to group tubulointerstitial features (type I) and separate those from biopsies with endarteritis (type II), because this may have therapeutic and prognostic implications. For routine diagnostic work, a grading of the severity of interstitial infiltrates and tubulitis does not seem helpful. As a third category, acute rejection with fibrinoid vascular necrosis...
(type III) stands out and indicates poor prognosis and treatment response. This approach has also been adopted by the revised Banff criteria (Banff Conference, 1997, unpublished data).

In summary, we demonstrated that certain histologic changes during acute rejection have an adverse effect on 6- and 12-mo serum creatinine levels and outcome, whereas others do not. The broad categories "acute rejection" and "vascular rejection" provide a less precise correlation (21). Additional studies evaluating acute rejection and allograft function should be designed and should pay particular attention to specific vascular lesions and assess the adequacy of the arterial sampling.

Acknowledgments

This work was supported in part by a grant from the United States Public Health Service (PO1-HL-18646). We thank Dr. M. J. Mihatsch (University of Basel, Switzerland) for critical review of the manuscript.

References