Apoptosis of Tubular Epithelial Cells in Donor Kidney Biopsies Predicts Early Renal Allograft Function

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Abstract. Acute renal failure (ARF) is a serious complication in the early postoperative period after kidney transplantation. In an effort to identify subjects at risk, several donor-, recipient-, and procedure-related factors have been studied. Because no morphologic parameter predictive of delayed graft function has been identified to date, this study was conducted to determine whether the number of apoptotic cells in donor biopsies obtained before engraftment is predictive of the development of posttransplant ARF. Donor biopsies of patients with “biopsy-proven” acute tubular damage but no signs of rejection (n = 23) showed significantly higher counts of apoptotic tubular epithelial cells when compared to patients with immediate transplant function (n = 44) or early rejection (n = 22). In all groups, a significantly higher percentage of apoptotic cells was found in the distal compared to the proximal tubule. The expression of bcl-2 and proliferating cell nuclear antigen was not different among the groups. Late allograft function was not affected by early ARF as serum creatinine values were similar in all three groups after 6 mo. These data suggest that the number of apoptotic renal tubular epithelial cells in donor biopsies before engraftment is predictive of the early postoperative course in patients undergoing kidney transplantation.

Renal transplantation is the preferred treatment for end-stage renal disease (ESRD). One of the most common early complications is post-ischemic acute renal failure (ARF), which has been reported to occur with an incidence of 20 to 50% (1,2). Cyclosporine immunosuppression, the duration of cold ischemia and anastomosis time (3–5), as well as donor factors such as age and cause of death (6,7), have been determined as important risk factors. Although the majority of patients recover, some authors have reported a negative effect of post-ischemic ARF on allograft and patient survival (8,9). It is well documented that renal tubular epithelial cells are the primary victims of prolonged hypoxia (10). The term “acute tubular necrosis” is also used for this scenario, suggesting that the predominant response to injury is necrosis, an unplanned, accidental cell death occurring in response to severe injury such as hypoxia, extremes of temperature, or toxins. Although necrosis clearly does occur, morphologic studies in humans over the past few decades have shown that this is not the only way of cell loss (11,12). Apart from necrosis, irreversibly damaged tubular cells die by apoptosis, a physiologic active form of programmed cell death that mediates the safe deletion of unwanted cells (13). Apoptosis is defined by highly characteristic and remarkably stereotypic morphologic changes such as condensation of nuclear heterochromatin, cytoplasmatic condensation, and cell shrinkage with retention of organelles (14). Apoptosis can be triggered by a variety of stimuli, including receptor ligation, growth factor withdrawal, exposure to chemotoxins, or even physical damage. Depending on the specific situation and the particular cell type, a variety of different internal signaling pathways can be initiated. However, these converge at certain control points into the execution phase of the program, where inhibitory or stimulatory cofactors like the family of bcl-2 proteins come into action. Some members such as bcl-2 or bcl-xL block apoptosis, whereas others such as bax or bak promote apoptosis.

Identification of patients at high risk for the development of posttransplant ARF could have important therapeutic implications. Unfortunately, conventional histologic evaluation of donor kidney biopsies cannot predict the early posttransplant clinical course (15). It was therefore the primary aim of our study to quantify the frequency of apoptosis in donor kidney biopsies and correlate these findings with the early clinical outcome in renal allograft recipients treated with cyclosporin A-based triple immunosuppression. Additionally, we measured the expression of the anti-apoptotic protein bcl-2. Finally, because cell turnover is determined not only by cell death but also by cellular proliferation, the expression of proliferating cell nuclear antigen (PCNA), a cell cycle regulatory protein that accounts for promotion of quiescent cells into mitosis, was also determined.

Materials and Methods

Patients

In January 1994, the practice to obtain random allograft biopsies immediately before engraftment was introduced at the University
Hospitla of Vienna. Until May 1997, 561 renal transplantations had been performed. We studied all cores of kidney biopsies that were large enough to allow the studies described below (92 cases obtained from 89 donors). These donors, all of whom were heart beating at the time of explantation, did not differ from the general donor population with regard to age, cold ischemia time, and the number of HLA mismatches (Table 1). The kidneys were perfused with the University of Wisconsin cold preservation solution. Depending on the posttransplant course, the transplant recipients, all on cyclosporin A-based triple immunosuppressive therapy without antibody induction therapy, were allocated to three different categories (Table 2). Group 1 patients \( (n = 44) \) exhibited immediate posttransplant excretory allograft function and no clinical signs of rejection during the first 7 d. Group 2 patients \( (n = 23) \) were dialysis-dependent for 7 to 21 d, and biopsy revealed acute tubular damage only, which was defined as tubular cell loss without replacement, flattening of the tubular epithelial cells, and loss of periodic acid-Schiff-positive brush-border staining in proximal tubuli. Group 3 patients \( (n = 22) \) were classified as those that experienced a biopsy-proven acute rejection episode during the first week after surgery. In seven subjects, additional mild signs of acute tubular damage were found. The remaining three patients had primary nonfunction of the graft and remained dialysis-dependent (anastomosis times 60, 60, and 30 min, donor age 66, 67, and 65 yr, respectively). Three of the patients in group 2 exhibited signs of mild cyclosporine toxicity such as isometric vacuolization, eosinophilic inclusion, and focal myocyte damage. On average, the mean cyclosporin A trough levels until discharge from the hospital were not 7 ng/ml, monoclonal FPIA assay; TDx, Abbott, Abbott Park, IL).

**Histologic Evaluation**

Wedge biopsies were obtained before engraftment and tissue was fixed in formalin and embedded in paraffin. A series of 30 consecutive, 4-µm sections was mounted on polylisin-precoated glass slides. Additional sections were stained with hematoxylin eosin (H&E), periodic acid-Schiff, trichrome (AFOG; acidic fuchsin orange G), and methenamine silver to allow histomorphologic grading of preexisting lesions. Pathologic examination of sections was carried out blinded to the posttransplant clinical course. Acute and chronic tubular damage as well as interstitial fibrosis, arteriolosclerosis, and mesangial matrix expansion were scored from 0 to 3 (0, none; 1, mild; 2, moderate; 3, severe pathology), and the percentage of obsolescent glomeruli was ranked from 1 to 5 (1, 5 to 15%; 2, 16 to 25%; 3, 26 to 35%; 4, 36 to 45%; 5, >45%). All biopsies obtained after engraftment were scored according to the Banff classification (16).

**Detection of Apoptotic Cells**

Because apoptosis could occur in a focal distribution, two tissue sections, 120 µm apart, were examined using TUNEL staining (terminal deoxynucleotidyl transferase [TdT]-mediated dUTP nick end labeling) of fragmented DNA (Boehringer Mannheim, Mannheim, Germany), as described by Gavrieli et al. (17). Briefly, paraffin-embedded sections were deparaffinized in xylene for 5 min, rehydrated through graded concentrations of ethanol, and washed in distilled water three times for 5 min. To inactivate endogenous peroxidase, the tissue sections were incubated for 10 min in 2% hydrogen peroxide and then rinsed three times in distilled water. To facilitate the penetration of enzymes and biotinylated deoxyuridine, the slides were subjected to 10 min of proteinase K (10 µg/ml) digestion, rinsed with water three times, and covered for 10 min with TdT labeling buffer (30 nM Trisma-base, pH 7.2, 140 mM sodium cacodylate, 1 mM cobalt chloride). The in situ nick end labeling of the fragmented DNA was performed by incubation with fluorescein-labeled TdT/biotinylated dUTP diluted in TdT buffer in a humid dark chamber at 37°C for 90 min (2 µl of TdT and 5 µl of biotinylated dUTP diluted in 40 µl of TdT buffer [Boehringer Mannheim]). An alkaline phosphatase-labeled anti-FITC antibody was then added for 60 min, and after 10 min of Fast Red incubation, which was used as chromogenic substrate for the alkaline phosphatase (Sigma, St. Louis, MO), the specimens were washed, counterstained with methylene green, and cover slips were mounted. The negative controls were incubated without TdT. Tissue specimens from tonsils and DNAase digested healthy control kidney specimens (1 µg/ml DNAase in buffer: Trisma base, pH 7.2, 140 mM sodium cacodylate, 4 mM MgCl₂) served as positive controls.

Since it has been argued that TUNEL staining is not completely specific for apoptosis (18), we counted the fraction of tubular cells in four fields of 0.0025 cm² of H&E-stained tissue sections in all biopsies that appeared apoptotic. Morphologic criteria suggestive of apoptosis were condensation of nuclear chromatin, convolution of the nuclear membrane, fragmentation of the cell nuclei, and shrinking of the cytoplasm. There was an overall good correlation between the number of apoptotic cells obtained by counting TUNEL- and H&E-stained tissue sections \( (r² = 0.80, P < 0.05 \text{ for proximal tubules, and } r² = 0.91, P < 0.05 \text{ for distal tubules}) \), although the fraction of apoptotic cells as determined morphologically was consistently smaller (30% and 20%).

**Detection of PCNA- and bcl-2-Positive Cells**

PCNA and bcl-2 protein-expressing cells were determined using a streptavidin-biotin peroxidase complex system and a monoclonal an-

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**Table 1.** Demographic data of the three groups of renal transplant recipients

<table>
<thead>
<tr>
<th>Group</th>
<th>Recipient Age (yr)</th>
<th>PRA (%)</th>
<th>MM</th>
<th>Donor Age (yr)</th>
<th>ICB/TR/O</th>
<th>Donor Creatinine (mg/dl)</th>
<th>CIT (h)</th>
<th>AT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48 ± 15</td>
<td>4 ± 8</td>
<td>2.0 ± 1.0</td>
<td>47 ± 16</td>
<td>21/19/4</td>
<td>1.03 ± 0.53</td>
<td>17 ± 7^b</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>2</td>
<td>48 ± 14</td>
<td>7 ± 13</td>
<td>2.2 ± 1.2</td>
<td>47 ± 13</td>
<td>13/8/2</td>
<td>1.05 ± 0.33</td>
<td>21 ± 8</td>
<td>35 ± 10</td>
</tr>
<tr>
<td>3</td>
<td>47 ± 12</td>
<td>6 ± 15</td>
<td>2.1 ± 1.4</td>
<td>55 ± 11</td>
<td>14/6/2</td>
<td>0.93 ± 0.36</td>
<td>20 ± 5</td>
<td>44 ± 10</td>
</tr>
</tbody>
</table>

^a Group 1 \( (n = 44) \) consisted of patients with immediate function of the transplanted kidney. Group 2 \( (n = 23) \) patients exhibited “biopsy-proven” posts ischemic acute tubular damage of 7 to 21 d duration, but no signs of rejection. Group 3 \( (n = 22) \) was classified as patients with biopsy-proven rejection within the first 7 d after transplantation. PRA, panel reactive HLA antibodies; MM, number of HLA A, B, and DR mismatches; ICB/TR/O, intracranial bleeding/trauma/other; CIT, cold ischemia time; AT, anastomosis time.

^b \( P < 0.05 \) group 1 versus group 2.
the interindividual coefficient of variation between the results was not significantly different among the groups for all parameters investigated. Overall, lesions were mild, perhaps due to the fact that donors in this series were on average quite young, although the biopsies of the three older donors of the patients with primary nonfunction exhibited a representative tissue specimen stained for bcl-2 and PCNA-positive cells.

Quantification of Apoptosis, PCNA, and bcl-2 Expression

The percentage of TUNEL-, bcl-2-, and PCNA-positive cells in the proximal and distal tubule as well as in the glomeruli were counted in eight fields of 0.0025 cm² size by two independent investigators. bcl-2 expression was also determined separately in parietal epithelial cells. The investigators were blinded for the donor and recipient data, and the interindividual coefficient of variation between the results was 6 ± 3%. Because no significant difference in the distribution of apoptosis was noted among the two slides 120 μm apart, the mean percentage of both readings was used for analysis.

Statistical Analyses

All data are given as mean ± SD. Differences among the patient groups and the cell types of bcl-2 expression were determined by factorial ANOVA and Scheffé F test for multiple comparisons. The unpaired t test and Bonferroni correction were used to calculate the differences in apoptosis and PCNA expression between proximal and distal tubular epithelial cells within each group. A linear correlation and Fisher transformation were used to calculate the linear relationship between two variables. A P value < 0.05 was considered statistically significant.

Results

Histopathologic Findings in Donor Biopsies and Posttransplant Clinical Course

As depicted in Table 3, semiquantitative histologic evaluation of donor biopsies revealed no significant differences among the groups for all parameters investigated. Overall, lesions were mild, perhaps due to the fact that donors in this series were on average quite young, although the biopsies of the three older donors of the patients with primary nonfunction yielded similar low scores (data not shown). Eight patients in group 1 experienced at least one acute allograft rejection episode, each after the first week but within the first 6 mo after engraftment, which led to allograft loss in three cases. The corresponding numbers for group 2 subjects were six patients and 0 allograft loss. Per definition, all patients in group 3 had rejection, leading to nephrectomy in three cases. Nonetheless, renal excretory allograft function 6 mo after engraftment was similar in the three groups (Table 2). The morphologic appearance as well as TUNEL staining of an apoptotic tubular epithelial cell is depicted in Figure 1, A and B. Figure 1, C and D, exhibits a representative tissue specimen stained for bcl-2 and PCNA, respectively.

Table 2. Postoperative serum creatinine (mg/dl)a

<table>
<thead>
<tr>
<th>Group</th>
<th>After 7 Days</th>
<th>After 30 Days</th>
<th>After 180 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.00 ± 0.78 (n = 44)b</td>
<td>1.75 ± 1.35 (n = 43)</td>
<td>2.13 ± 0.85 (n = 41)</td>
</tr>
<tr>
<td>2</td>
<td>7.57 ± 2.60 (n = 23)</td>
<td>1.71 ± 0.53 (n = 23)</td>
<td>1.51 ± 0.42 (n = 23)</td>
</tr>
<tr>
<td>3</td>
<td>7.85 ± 2.51 (n = 22)</td>
<td>6.47 ± 2.86 (n = 19)c</td>
<td>2.1 ± 1.4 (n = 19)</td>
</tr>
</tbody>
</table>

a Group 1 (n = 44) consisted of patients with immediate function of the transplanted kidney. Group 2 (n = 23) patients exhibited “biopsy-proven” posts ischemic acute tubular damage of 7 to 21 d duration, but no signs of rejection. Group 3 (n = 22) was classified as patients with biopsy-proven rejection within the first 7 d after transplantation.

b P < 0.05 group 1 versus group 2 and group 3.

c P < 0.05 group 3 versus group 1 and group 2.

Table 3. Histopathology of donor kidney biopsiesa

<table>
<thead>
<tr>
<th>Group</th>
<th>TA</th>
<th>TC</th>
<th>II</th>
<th>IF</th>
<th>AS</th>
<th>ME</th>
<th>GL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 ± 0.6</td>
<td>0.3 ± 0.6</td>
<td>0.1 ± 0.3</td>
<td>0.7 ± 0.6</td>
<td>0.4 ± 0.7</td>
<td>0.1 ± 0.3</td>
<td>0.6 ± 1.3</td>
</tr>
<tr>
<td>2</td>
<td>1.1 ± 0.5</td>
<td>0.8 ± 0.7</td>
<td>0.3 ± 0.5</td>
<td>0.9 ± 0.7</td>
<td>0.8 ± 0.7</td>
<td>0.6 ± 0.5</td>
<td>0.9 ± 1.5</td>
</tr>
<tr>
<td>3</td>
<td>1.1 ± 0.4</td>
<td>0.3 ± 0.5</td>
<td>0.1 ± 0.3</td>
<td>0.6 ± 0.5</td>
<td>0.8 ± 0.9</td>
<td>0.3 ± 0.6</td>
<td>0.8 ± 0.9</td>
</tr>
</tbody>
</table>

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Quantification of Apoptosis

In all groups, apoptosis was rarely observed in the glomerular and interstitial compartment, whereas it was uniformly more common in distal compared to proximal tubular epithelial cells \( (P < 0.05 \text{ in all three groups}) \). As shown in Figure 2, group 2 patients with post-transplant ARF but no rejection had more than twice as many apoptotic cells as group 1 and 3 subjects \( (P < 0.05, \text{ group 1 versus group 2}) \). Biopsies of patients with primary nonfunction showed similar numbers of apoptotic cells as group 2 individuals \( (\text{mean TUNEL-positive proximal and distal tubular cells } 1.7 \pm 1.4\% \text{ and } 2.7 \pm 0.5\%, \text{ respectively}) \). Although cold ischemia time was significantly longer in group 2 patients, regression analysis failed to show a significant correlation between cold ischemia time and the number of apoptotic cells in either proximal or distal tubule. This was true for the whole patient group as well as for group 2 patients only. There was no significant correlation between TUNEL-positive cells and the extent of early graft dysfunction in group 2 patients.

bcl-2 and PCNA Expression

As shown in Figure 3, bcl-2 expression was most prominent in the distal tubule. Glomerular parietal epithelial cells and cells inside the glomerular tuft only occasionally stained positive. There was no statistical difference among the patient groups. Since very few glomerular and interstitial cells stained positive for PCNA, only the tubular compartment was quantified. Interestingly, PCNA was detected mainly in proximal tubular cells (Figure 4), although in the three patients with primary nonfunction, the expression of the protein in proximal tubule epithelial cells was reduced \( (\text{proximal tubules } 4.9 \pm 1.6\%, \text{ distal tubules } 5.7 \pm 2.4\% \text{ of all cells}) \). When we performed PCNA staining on uninvolved sections of a tumor nephrectomy kidney, only 0.1 \( \pm 0.3\% \text{ of the cells expressed this protein}. \) There was no correlation between the number of PCNA-positive cells and cold ischemia time.

In three donors, biopsies from both the right and left kidney were available. TUNEL, bcl-2, and PCNA staining results were similar in both kidneys, as was the posttransplant course of the six recipients.
Discussion

ARF is the most common complication in the early postoperative period after kidney transplantation. Although it remains a matter of controversy whether patient and/or allograft survival are negatively affected by ARF, it has been proposed recently that allograft rejection might be triggered by intrarenal changes induced by ischemia and/or ARF (19). In any case, the clinical management of a patient with delayed allograft function is more complicated. The administration of cyclosporin A beneficially influences 1-yr allograft survival, possibly due to better immunosuppression, but has been shown to further increase the incidence and even prolong the duration of posttransplant ARF (2). In our study, cyclosporin A trough levels were similar among all patient groups studied, and hence the variability in early clinical outcome cannot be accounted for by a toxic drug effect. Cold and warm ischemia time as well as recipient factors like the percentage of panel reactive cytotoxic antibodies before transplantation have also been reported to be
important risk factors for the development of delayed allograft function. However, a prediction of the risk for ARF based on these data is still not possible, and hence donor-related factors such as age, cause of death, or hemodynamic instability during the procurement phase have also become a matter of interest (4,8). In our series of patients, we were only able to demonstrate that an increased duration of cold ischemia time was associated with the development of ARF, whereas all other mentioned parameters were not. It therefore seems reasonable to include a histologic evaluation of a biopsy core obtained before engraftment into the risk stratification management. Despite reports that kidneys with a normal glomerular structure are more likely to gain immediate function after engraftment (20), negative histologic predictors have not been established. Our results using conventional evaluation of the biopsy specimen confirm these data, although this may possibly be due to the subtle changes occurring and the overall good histologic grading.

As mentioned previously, the term acute tubular necrosis is used to describe the histopathologic correlate of posttransplant ARF. Although many cells die by necrosis, some are initially only damaged sublethally and are later removed by apoptosis (21,22). On the basis of these findings, we determined the percentage of apoptotic proximal and distal tubular epithelial cells in donor kidney biopsies taken immediately before engraftment and correlated the results to the postoperative course of the recipients. Apoptosis was determined by the TUNEL technique, and because this procedure is reportedly not entirely specific for apoptosis (18), we also counted the fraction of tubular cells of H&E-stained tissue sections, which appeared apoptotic on a morphologic basis as well. As has been reported by others, a good correlation between both methods was observed (23).

As has described earlier by Schumer et al. (21) and Beeri et al. (24) for hypoxic rat kidneys, apoptosis is more common in distal compared to proximal tubular cells. This is surprising, because usually the latter are felt to be more susceptible to ischemic injury. However, this statement has thus far only been confirmed for necrotic cell death after severe injury and the response to more subtle damage might well be different. In support of this hypothesis, we found no correlation between what is probably the most potent insult, cold ischemia time, and the rate of apoptosis.

The main result of our investigation was that patients with delayed allograft function and no histologic signs of rejection have a significantly higher rate of apoptotic cells compared to recipients with immediate graft function, or patients with allograft failure due to early rejection. Unfortunately, we cannot extract from our data whether the damage leading to the initiation of programmed cell death was already induced when the kidneys were still in situ or during the preservation period. However, as already mentioned, cold ischemia time was, on average, significantly longer in patients with a high percentage of apoptotic cells, but no correlation between cold ischemia time and the percentage of TUNEL-positive cells was found. These data suggest that both factors contribute to the pathogenesis of delayed graft function. The total number of apoptotic cells and the observed differences between the patient groups appears rather low (0.5 to 2.5%). However, apoptotic cells are phagocytosed very efficiently by resident macrophages. It has been reported for smooth muscle and endothelial cells that this process takes only minutes to a few hours (25). Because apoptotic cells disappear rapidly from the tissue, the low absolute rate of apoptosis may still be responsible for extensive cell loss (13,26).

Apoptosis is regulated by various internal mechanisms. One of them is the relative expression of pro- and anti-apoptotic proteins, such as bax and bcl-2, which are reportedly upregu-
lated in regenerating renal tubules following ischemia (27). In our study, we determined bcl-2 expression and were unable to find a significant difference in the expression of this anti-apoptotic protein between our patient subgroups. In agreement with the findings of Nakopoulou et al. (28), bcl-2 expression was higher in the distal compared to the proximal tubular compartment. Because bcl-2 is only one of the numerous important apoptosis regulatory mediators, it will be the goal of further studies to determine the ischemia-induced alterations of the apoptosis regulatory system.

Cell turnover within a tissue compartment is determined not only by cell death, but also by proliferation. Under normal circumstances, renal tubular cells are quiescent and do not readily divide in response to growth factors. However, after an ischemic insult, surviving renal tubular cells reenter the cell cycle (as evidenced by PCNA expression) and replicate, thus replacing irreversibly injured cells (29,30). Although little is known about the complex series of events mediating this process, cell regeneration commences immediately after the insult has occurred (30). It is unclear whether PCNA expression during cold storage occurs, but the relatively high percentage of PCNA-positive proximal tubular epithelial cells in our study provides support to the notion that the organ is already damaged when still in situ in the donor. In experimental ARF, Shimizu and Yamanaka (22) also demonstrated that the proximal tubule is the major site of cellular division in the repair phase after tubular injury. The importance of the proliferative response for recovery from injury can be appreciated, as PCNA expression in the three patients with primary non-function of the graft was much lower than in the other groups.

In summary, our data suggest that the number of apoptotic tubular epithelial cells in donor kidney biopsies obtained before engraftment predicts early graft function. Interventions to decrease apoptosis-inducing stimuli before transplant might therefore prove beneficial in avoiding this serious complication of renal transplantation.

Acknowledgments

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References


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