

Systematic Kidney Biopsies After Acute Allograft Pyelonephritis

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Abstract

Objectives: Scarce data exist regarding the effect of acute graft pyelonephritis on kidney histology after a kidney transplant. This study sought to assess the kidney histology at 1 month, and kidney function at 1 year, after acute graft pyelonephritis in kidney transplant patients.

Materials and Methods: All kidney transplant patients with acute graft pyelonephritis between October 2006, and December 2008, underwent a kidney biopsy 1 month later (n=28). Histologic findings were compared with those observed in a control group (n=28) who underwent a protocol kidney biopsy at 1 year posttransplant and did not present with acute graft pyelonephritis. Patients were matched according to age, sex, and immunosuppressive regimen.

Results: Kidney function was impaired by the acute graft pyelonephritis episodes at the time of biopsy. In 40% of patients, the estimated glomerular filtration rate did not return to baseline by 1 month after acute graft pyelonephritis and remained impaired thereafter. Three patients had features of acute rejection. Tubulitis was seen more frequently in the acute graft pyelonephritis group, especially in patients in whom estimated glomerular filtration

rate did not completely recover by 1 month after acute graft pyelonephritis. Patients with acute graft pyelonephritis who had inflammatory infiltrate of > 20% 1 month after acute graft pyelonephritis had worse kidney function 1 year later.

Conclusions: After transplant, when kidney function remains impaired 1 month after acute graft pyelonephritis, kidney biopsies allowed graft rejection diagnosis and predicted kidney function recovery.

Key words: Kidney transplant, Pyelonephritis, Tubulitis, Acute rejection, Kidney function

Introduction

Urinary tract infection is a common complication observed after kidney transplant. Its incidence ranges from 17% to 80%.^{1,2} Acute graft pyelonephritis (AGPN) occurs in 8.8% to 26% of patients after a kidney transplant.^{3,4} Lower and upper urinary tract infections are related to bacterial exposure, surgical procedure, previous asymptomatic bacteriuria, and immunosuppressive therapy.^{5,6}

The effect of posttransplant pyelonephritis on the kidney allograft's long-term function and survival remains controversial. Abbott and associates have shown that urinary tract infection occurring late after a kidney transplant is associated with increased morbidity and mortality.⁷ Giral and associates identified early acute pyelonephritis as an independent risk factor for renal allograft loss.⁸ Similarly, Pellé and associates found that AGPN occurring within the first 3 months after a kidney transplant has a detrimental effect on graft function.⁴ Finally, Fiorante and associates recently found that AGPN did not impair long-term kidney allograft

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function.⁶ Ozdemir and associates suggested that tubulointerstitial nephritis may induce kidney-allograft rejection.⁹ Similarly, Audard and associates found that acute rejection episodes may occur soon after AGPN.¹⁰ After infection of the kidney, the immunostimulatory response may induce acute rejection that could be subclinical.¹¹

This study sought to assess the kidney histology at 1 month after AGPN in 28 kidney transplant patients. The histologic findings were compared with those observed in a control group of kidney recipients who had undergone protocol kidney allograft biopsies, and who did not present with AGPN within the 6 months before the biopsy.

Materials and Methods

Patients

All kidney transplant patients attending the Department of Nephrology and Organ Transplantation, who presented with AGPN between October 2006, to December 2008, were included in the study (n=28) (AGPN group). The clinical trial was approved by the ethics committee of the hospital before the study began, and the protocol conformed with the ethical guidelines of the 1975 Helsinki Declaration. After having given their written, informed consent, all patients underwent a kidney allograft biopsy 1 month after the AGPN whatever the renal function was. The median time between kidney transplant and the kidney allograft biopsy episode was 11.5 months (range, 2 to 205 mo). Histologic findings were compared with those observed in a control group who underwent a protocol kidney biopsy at 1 year after the transplant, and who did not present with AGPN within the 6 months before the biopsy (n=28). Both groups were matched according to age, sex, and immunosuppressive regimen (induction therapy and main immunosuppressant, ie, cyclosporine, tacrolimus, or belatacept). In all patients, a double-J ureteric stent inserted during the kidney transplant was removed 6 weeks after the transplant. In all patients, *Pneumocystis jiroveci* prophylaxis based on trimethoprim-sulfamethoxazole was implemented for 6 months.

Diagnosis of acute graft pyelonephritis episodes

The diagnosis of AGPN was based on fever and a urinary basis count of more than 10⁵ colony-forming

units (cfu)/mL combined with a urinary leukocyte count of more than 10⁴/mL, or a single urinary count of more than 10⁶ cfu/mL. All patients with AGPN were hospitalized and received antimicrobial agents against urinary bacteria, first intravenously until apyrexia was achieved, and then orally for 2 to 3 weeks.

Pathologic analysis

For light microscopy examination, biopsy specimens were fixed in Bouin solution, embedded in paraffin, cut into 2- μ m thick sections, and stained with light-green trichrome, periodic acid-Schiff, and hematoxylin and eosin stains. All biopsies had more than 10 glomeruli, and at least 2 arterial sections. All biopsies were scored according to the 2007 Banff classification.¹² Routine immunofluorescence studies used polyclonal antibodies to C3, immunoglobulins (Ig)A, IgG, and IgM. C4d immunostaining also was performed. Inflammatory infiltrate was considered to be significant if it involved $\geq 5\%$ of the kidney biopsy. In case of significant inflammatory infiltrate (semiquantitative analysis), anti-CD3, and anti-CD20 staining was performed.

Parameters studied

We collected the following parameters in patients: age at transplant, sex, the number of kidney transplants, the cause of end-stage kidney disease, panel-reactive antibodies at transplant, use of induction therapy after transplant, immunosuppressive regimen immediately after transplant, and the time of AGPN in the AGPN group, and the time of kidney biopsy in both groups. We also assessed the number of acute-rejection episodes, and their type (ie, steroid-sensitive, steroid-resistant, or antibody-mediated rejection). Kidney function was formula¹³ at 6, 3, and 1 month before the biopsy, at the time of a pyelonephritis episode (in the AGPN group only), at the time of the kidney biopsy, and at 3, 6, and 12 months after the biopsy.

Statistical analyses

Data are presented as means $\pm$ standard deviations or medians (ranges). Quantitative parameters were compared using the Fisher exact test. Qualitative parameters were compared using the Friedman test for repeated measurements, the Wilcoxon test, and the Mann-Whitney *U* test. *P* values below .05 were considered statistically significant.

Results

Patient characteristics

The patient characteristics did not differ between groups (Table 1). Before the AGPN, 5 patients in each group experienced a steroid-sensitive acute rejection episode. There were no significant differences in immunosuppressant type or dosages between the time of the AGPN episode, and the kidney biopsy in the AGPN group (data not shown), or between the AGPN group and the control group at the time of the kidney biopsy.

Table 1. Patient Characteristics

Patient Characteristics	AGPN Group (n=28)	Control Group (n=28)	P Value
Recipient age (y)	46.5 [23-65]	49 [25-69]	NS
Sex (male/female)	12/16	12/16	NS
No. of previous transplants	1 [1-2]	1 [1-3]	NS
Median PRA at transplant (%)	0 [0-85]	0 [0-92]	
Cause of ESRD			
Glomerular disease	11	11	NS
Urological disease or interstitial nephropathy	9	2	
Genetic disease	6	9	
Other	2	6	
Acute rejection before kidney biopsy (%)	17.9%	17.9%	NS
Immunosuppressive regimen at transplant			
Induction therapy	26	26	NS
RATG/anti-IL2R	8/18	8/18	NS
CNIs	18	18	NS
Belatacept	7	7	NS
mTOR inhibitors	5	3	NS
MPA	22	28	NS
Steroids	25	28	NS

Abbreviations: AGPN, acute pyelonephritis glomerulonephritis; CNIs, calcineurin inhibitors; ESRD, end-stage renal disease; IL2-R, interleukin-2 receptor; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; NS, not significant; PRA, panel-reactive antibodies; RATG, rabbit anti-thymocytes globulins.

Description of acute pyelonephritis episodes

The median time between kidney transplant and the pyelonephritis episode was 11.5 months (range, 2 to 205 mo). The AGPN episode occurred in 50% and 89% of patients within the first and second year after transplant. Seven patients (25%) had experienced 1 or more previous allograft AGPN: 2.3 ± 1.2 episodes on average. The most frequent bacteria were *Escherichia coli* (n=18), *Pseudomonas aeruginosa* (n=2),

and *Enterobacter aerogenes* (n=2). No microorganisms were found in the urine or blood samples of 2 patients. In 6 patients, microorganisms detected in the urine also were found in the blood. After the diagnosis of AGPN, all patients received antibiotics for a median length of 18 days (range, 10 to 26 d).

Effect of acute graft pyelonephritis on kidney function and histology

In the control group, no significant changes in eGFR were observed during follow-up (Figure 1). Compared to 6, 3, and 1 month before the acute pyelonephritis episode, eGFR significantly decreased at the time of the pyelonephritis ($P < .0001$). It significantly increased at the time of the kidney biopsy ($P < .0004$), and then stabilized at 1 ($P < .0004$), 3 ($P < .002$), 6 ($P < .004$), and 12 months later ($P < .0004$). At 1 month after AGPN, eGFR returned to baseline values in 17 of 28 patients (60.7%). Graft function remained significantly worse during the first year after the pyelonephritis episode in the group in whom eGFR did not return to baseline values after 1 month (Figure 2).

Figure 1. Outcome of Glomerular-Filtration Rate Before and After the Kidney Biopsy in the Acute Pyelonephritis and Control Groups

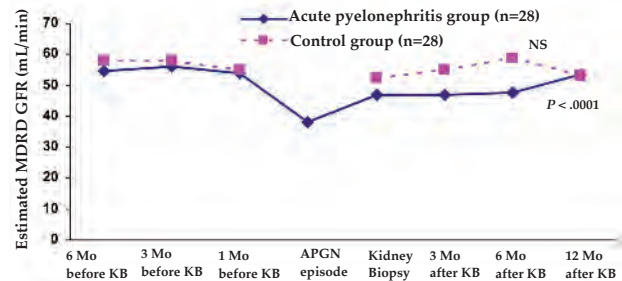
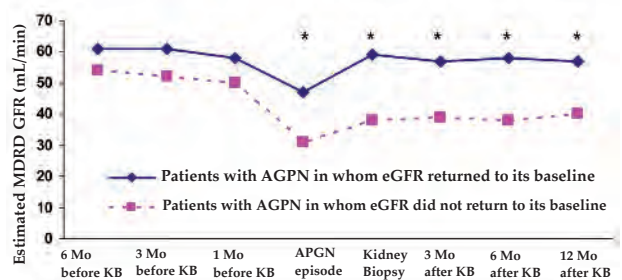


Figure 2. Outcome of Glomerular-Filtration Rate in Patients in Whom Kidney Function Returned, or Not, to its Baseline Values by 1 Month After Acute Allograft Pyelonephritis



As depicted in Table 2, only tubulitis (0.39 ± 0.78 vs 0.07 ± 0.26 ; $P < .06$) and arteriolar hyaline-thickening (1.09 ± 0.94 vs 0.64 ± 0.68 ; $P < .09$) scores

tended to be higher in the AGPN group, compared with results obtained from the control group. Tubulitis score were significantly lower in patients in whom eGFR returned to baseline values by 1 month after AGPN compared with patients in whom eGFR did not (0.87 ± 1.1 vs 0.13 ± 0.35 ; $P < .04$).

Table 2. Histopathologic Patterns in the Acute-Allograft Pyelonephritis and Control Groups

Kidney Lesions	AGPN Group (n=28)	Control Group (n=28)	P Value
Glomerulitis	0.09 ± 0.29	0.25 ± 0.7	NS
Mononuclear-cell interstitial inflammation	0.77 ± 0.97	0.36 ± 0.89	NS
Tubulitis	0.39 ± 0.78	0.07 ± 0.26	.06
Initial arteritis	0 ± 0	0 ± 0	NS
Arteriolar hyaline thickening	1.09 ± 0.94	0.64 ± 0.68	.09
Allograft glomerulopathy	0 ± 0	0.11 ± 0.31	NS
Interstitial fibrosis	1 ± 1.04	0.82 ± 0.67	NS
Tubular atrophy	1 ± 1.04	0.93 ± 0.6	NS
Vascular fibrous intimal thickening	1.05 ± 0.97	0.88 ± 0.88	NS
Mesangial matrix increase	0.39 ± 0.5	0.36 ± 0.49	NS

Abbreviations: AGPN, acute pyelonephritis glomerulonephritis; NS, not significant

In the AGPN group, kidney biopsies revealed signs of acute rejection in 3 patients, in whom eGFR did not return to baseline values by 1 month after AGPN ($P < .05$). In the first of these patients, eGFR decreased during the AGPN episode, and then increased at the time of the kidney biopsy. This patient had borderline acute rejection, which was not treated. In the second patient, eGFR decreased during the AGPN episode, and then stabilized by 1 month later. The patient showed features of cellular acute rejection and required steroid pulses. In the third patient, eGFR decreased during the AGPN episode, and then decreased again at the kidney biopsy. This patient had features of both cellular and humoral rejection; C4d staining was negative and donor-specific antibodies were found to be positive for the first time. Steroid pulses, plasmapheresis, and intravenous immunoglobulins were given. In the control group, none of the patients had any histologic patterns of acute cellular or humoral rejection.

In the AGPN group, 16 of the 28 patients (57%) had a significant polymorphic inflammatory infiltrate, whereas it was only observed in 4 of the 28 patients (14.3%) from the control group ($P < .0007$). In the AGPN group, the median inflammatory infiltrate was evaluated to be 7.5% (range, 0% to 100%), and

was composed of 68% T cells and 32% B cells. In the control group, the median inflammatory infiltrate was 0% (range, 0% to 35%). Within the AGPN group, the time since transplant, the type of immunosuppressive therapy, and eGFR at 3, 6, and 12 months after the kidney biopsy, did not differ significantly between patients who had $\geq 5\%$, and those who had $< 5\%$ inflammation infiltrate (data not shown).

In addition, we evaluated, within the AGPN group, the effect of long-term kidney function on having $> 20\%$ inflammation infiltrate in the kidney biopsy. The time since transplant to the AGPN episode, and the immunosuppressive therapy, dosage, and levels, did not differ significantly between patients with inflammatory infiltrate that was either greater or less than 20% (Table 2). Kidney function during the pyelonephritis episode, and at 3, 6, and 12 months after the kidney biopsy, 3 was better in patients who had an inflammatory infiltrate $\leq 20\%$.

Table 3. Comparison Between Patients With an Inflammatory Infiltrate Greater Than 20% and Those Less Than or Equal to 20%

Variable	II $\leq 20\%$ (n=17)	II $> 20\%$ (n=11)	P Value
Time since transplant (mo)	16 (2-205)	9.5 (3-45)	NS
CNIs at kidney biopsy (%)	47%	81%	.1
Mean cyclosporine C2 level (ng/mL)	703 ± 141	863 ± 345	NS
Mean tacrolimus trough level (ng/mL)	5 ± 1.3	6.4 ± 2.9	NS
Mean MPA dose (mg/kg/d)	21.9 ± 4.2	20.9 ± 15.4	NS
Mean steroid dose (mg/kg/d)	0.12 ± 0.1	0.13 ± 0.06	NS
eGFR (mL/min)			
6 months before AGPN	52.7 (34.7-92)	50.85 (38-87)	NS
3 months before AGPN	56 (29-105)	50.8 (38-90)	NS
1 month before AGPN	58 (29-101)	45.3 (31-61)	NS
at AGPN	49.2 (19-89)	30.75 (11.5-53)	.06
at kidney biopsy	48 (25-97)	36.5 (16-68)	.08
3 months after KB	50 (19-92)	37 (25-59)	.04
6 months after KB	52.1 (17-89)	37.5 (18-79)	.1
12 months after KB	57 (18-89)	38.2 (12-74)	.1

Abbreviations: AGPN, acute graft pyelonephritis; C2, 2-hour concentrations; CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate; II, inflammatory infiltrate; KB, kidney biopsy; MPA, mycophenolic acid; NS, not significant.

Kidney allograft and patient outcomes

Two-year patient and graft survivals were 96.4%/96.4% and 93%/93% in the AGPN and control

groups. We observed 2 graft losses in the AGPN group, because of steroid-resistant acute humoral rejection and chronic allograft nephropathy. In the control group, 2 graft losses also were reported, 1 because of a sudden kidney-artery, and the second because of a BK nephropathy. During the 2-year follow-up, 1 patient from the AGPN group died with a functioning graft 20 months after the AGPN episode from sepsis and multiorgan failure, and another patient from the control group died from lung cancer.

Discussion

Similar to previous reports, AGPN mainly occurred within the first year (median, 11.5 mo), in women (57%), mainly in patients who received a transplant for a urologic disease and/or an interstitial nephropathy (32%).^{4,14} As previously observed,¹⁵ gram-negative microorganisms, and particularly, *Escherichia coli*, were the most frequently isolated species.

Scarce data exist regarding the effect of acute pyelonephritis episodes after a kidney transplant on long-term kidney function, kidney histology, occurrence of an acute rejection episode, and allograft and patient survival rates. In the present study, there was a significant decrease in eGFR during the AGPN episode. Nevertheless, no significant difference in kidney function was observed between patients with or without AGPN. Then, eGFR returned to baseline values by 1 month later in only 60% of patients. Kidney function was significantly better during AGPN and thereafter in these patients, compared with those in whom eGFR did not return to baseline. Rice and associates have reported that *E. coli*-induced pyelonephritis is responsible for acute allograft injury.¹⁵ By means of a multivariate analysis, AGPN has been identified by Pellé and associates as an independent risk factor associated with a decline in kidney function.⁴ Conversely, Fiorante and associates found that AGPN does not impair long-term kidney allograft function.⁶

The mechanisms of impaired kidney function after AGPN are not fully understood. It has been suggested that AGPN may be a trigger for acute rejection. Indeed, Audard and associates have reported that among 9 kidney transplant patients with AGPN who had undergone a kidney biopsy less

than 1 month after pyelonephritis, two (22%) had features of acute rejection.¹⁰ Conversely, the results of a large series including 1387 consecutive primary kidney transplant patients did not support the hypothesis that AGPN may trigger an acute-rejection episode.⁸ But no systematic kidney-allograft biopsies were performed. In the present study, among the 28 kidney-transplant patients with AGPN, features of acute rejection were observed in 3 patients (10.7%), while no case of acute rejection was diagnosed in the control group ($P = \text{NS}$). All acute rejection episodes occurred in patients in whom eGFR did not return to baseline values at 1 month after AGPN.

We further studied histologic characteristics. The proportion of patients with significant inflammatory infiltrate ($> 5\%$ of the total biopsy) was significantly higher in patients with AGPN (57%) compared with controls (14%). It was mainly composed of CD3-positive cells. In addition, during the year after AGPN, kidney function was worse in patients who had an inflammatory infiltrate $> 20\%$. We can speculate that this inflammatory infiltrate, persisting 1 month after AGPN, is the consequence of the immune response induced by the AGPN, and may impair long-term kidney function. Indeed, in addition to the interstitial scars caused by AGPN, which result in a reduced number of functioning nephrons, a bacterial infection may activate the immune system, leading to acute or chronic rejection. It has been shown, in vitro, that direct activation of renal cells via toll-like receptors (TLR) occurs by recognizing invading pathogens during renal infection. Tubular epithelial cells, as well as resident interstitial macrophages or dendritic cells, become activated via TLR.¹⁶ Toll-like receptor-4-deficient mice have interstitial neutrophil infiltration decreased, in a model of bacterial pyelonephritis,¹⁷ and were resistant to endotoxin-induced acute renal failure.¹⁸ Furthermore, bacterial infections of the kidney induce secretion of defensins, small antimicrobial peptides from tubular epithelial cells.¹⁶ Interestingly, β -defensin-2 has been shown to be an endogenous ligand for TLR4 and to induce dendritic cell activation.¹⁹ Hence, TLR ligands could activate the T-cell response, leading to inflammatory infiltrate and sometimes to acute rejection. T-cell activation may be enhanced by AGPN-induced chemokine production, such as interleukin-8 and epithelial cell-derived neutrophil-activating protein 78.²⁰

In the present study, only 1 graft was lost after an AGPN episode because of chronic allograft nephropathy and repeated AGPN episodes. However, the follow-up was short and our sample was too small to allow detection of any difference in graft survival between patients with or without AGPN. Data from the United States Renal Data System (USRDS) suggest that urinary tract infections that occur more than 6 months after transplant are associated significantly with an increased risk of subsequent death, as assessed in Cox proportional hazards regression model (adjusted hazard ratio, 2.93; 95% CI: 2.22-3.85) and graft loss (adjusted hazard ratio, 1.85; 95% CI: 1.29-2.64).¹ Giral and associates found that when AGPN occurs during the first 3 months after transplant, it was a significant independent risk factor for graft loss (RR = 3.6, 95% CI: 1.4-9.2; $P < .007$).⁸ Pellé and associates found that AGPN did not alter graft survival.⁴ Finally, Audard and associates found that actuarial allograft survival was significantly lower in patients with AGPN compared with controls.¹⁰

In summary, worse kidney function, acute rejection episodes, and tubulitis were observed in patients in whom eGFR did not return to its baseline values within 1 month after AGPN. Elevated interstitial infiltrate was associated with worse long-term kidney function. Hence, as previously suggested by Audard and associates,¹⁰ we recommend performing kidney allograft biopsies in patients in whom kidney function remains impaired at 1 month after AGPN. Prospective studies are required to assess whether treating patients with tubulitis and interstitial infiltrate in this setting improves long-term kidney function and, consequently, kidney allograft survival.

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