Late Recurrent Urinary Tract Infections May Produce Renal Allograft Scarring Even in the Absence of Symptoms or Vesicoureteric Reflux

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Background. The significance of late urinary tract infections (UTIs) after renal transplantation and their association with scarring and graft dysfunction remains controversial. We sought to define the prevalence of renal scarring in allograft recipients with a history of late recurrent UTIs, to determine whether the presence of vesicoureteric reflux (VUR) confers an increased risk of scarring and to establish whether scarring correlates with graft dysfunction.
Methods. Among 307 renal allograft recipients, we identified 56 (18%) with late recurrent UTIs (≥3/year). A total of 32 patients had undergone further investigation by both 2,3 dimercapto-succinic acid single-photon emission computed tomography (99mTc-DMSA SPECT) scan and micturating cystourethrogram (MCUG).
Results. Of the 32 patients, 24 (75%) had scars on 99mTc-DMSA SPECT and 15 (47%) had reflux on MCUG. Thirteen of these 15 patients with reflux (87%) had scars, although there was no significant correlation between number of scars and degree of reflux. Eleven of 17 patients (65%) with UTIs but without VUR had scars, as did 12 of 14 (86%) with previous graft pyelonephritis. The pattern of scarring (typically multiple focal cortical defects) suggested infection as the cause. This pattern was not seen in a contemporary cohort with vascular occlusions and was rarely seen in patients with chronic allograft nephropathy. Scarring was not associated with inferior graft survival (median follow-up, 15 years).
Conclusions. In patients with late UTIs, renal scarring is a frequent finding. Scarring may occur even in asymptomatic patients without VUR. The lack of an effect on graft survival may reflect successful intervention with prophylactic antibiotics and surveillance urine cultures. Late recurrent UTIs may be damaging to renal allografts, even in the absence of reflux.

Keywords: Kidney transplantation, Urinary tract infection, Vesicoureteric reflux; DMSA SPECT scan, Scarring.

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Urinary tract infection (UTI) is a common complication after renal transplantation with a reported incidence ranging from 6% to 83% (*1–6*). In the first 3 months post-transplantation, infection often presents as overt pyelonephritis and is associated with relatively high rates of bacteremia (*7*, *8*). Later episodes are often subclinical, manifesting as asymptomatic bacteriuria detected only by routine urine screening (*1*, *3*).

The significance of late urinary tract infections remains an area of considerable controversy. Studies of children with vesicoureteric reflux (VUR) have suggested that, for native kidneys at least, scarring due to urinary tract infection rarely occurs beyond the age of 5 years (*9*). Adult kidneys have thus been considered largely unsusceptible to scarring (*9*, *10*). As a consequence, recurrent urinary tract infections have not been generally accepted as a cause of late graft dysfunction (*1*, *2*, *7*, *11–13*), although this assertion appears to be based on only a handful of small studies (*1*, *14–16*).

A recent review of U.S. registry data (*17*) has challenged this view and suggests that late UTIs are not benign but rather are associated with an increased risk of death and graft loss. However, due to the inherent limitations of registry data, it is difficult to draw definitive conclusions from this report. Patient death in that study was predominantly from cardiovascular rather than infective causes and while rates of graft loss were certainly higher in those with late UTIs, rates of graft loss due specifically to infection were not significantly different. The authors concede that they cannot therefore be certain as to whether this was a direct effect or whether UTIs were simply a marker for serious underlying disease.

Another related area of uncertainty concerns the significance of reflux in transplanted kidneys and in particular whether the presence of VUR increases the risk of urinary tract infections or portends poorer graft outcome. Reflux into the graft is certainly a frequent finding with an incidence of up to 86% (*12*, *18–22*). Antireflux techniques for ureteric reimplantation, such as submucosal tunnelling, reduce but do not eliminate the risk of VUR (*20*). The prevailing view seems to be that reflux is a benign condition which does not compromise kidney function or predispose to recurrent UTIs (*12*, *19*, *23*). Indeed, some believe it to be so inconsequential as to suggest that the additional operative time associated with antireflux techniques may not be justified (*23*, *24*). Other investigators, however, have sounded a more cautionary note, reporting declining kidney function associated with reflux (*21*, *25*).

The aim of this study was to try to resolve some of these issues. Specifically, we sought to define the prevalence of renal

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scarring in allograft recipients with a history of late recurrent UTIs, to determine whether the presence of VUR confers an increased risk of renal scarring and finally to establish whether the presence of renal scarring correlates with graft dysfunction.

PATIENTS AND METHODS

To address these aims, we retrospectively reviewed the medical records of 307 renal allograft recipients transplanted at the Royal Free Hospital, London from 1976 to 1994 in order to identify patients with a history of late UTIs (occurring >6 months posttransplantation). As part of our standard practice during this period, all patients attending the transplantation outpatient clinic were routinely screened for urinary tract infection. We defined UTI as $>10^5$ colony forming units of a single organism cultured from midstream urine. Recurrent UTIs were defined as three or more positive urine cultures in a year.

A total of 56 patients (18%) were identified as having had late recurrent UTIs. In most cases UTIs were asymptomatic, but patients with lower tract symptoms or pyelonephritis were included in the study.

In all, 32 patients had undergone further investigation by both 99mTc 2,3 dimercapto-succinic acid single-photon emission computed tomography (99mTc-DMSA SPECT) scan and micturating cystourethrogram (MCUG). This group forms the basis of our report. The remaining patients declined investigation and are excluded from our analysis.

99mTc DMSA SPECT

99mTc-DMSA SPECT imaging was used to detect the presence of renal cortical scars. This technique is generally considered to be the "gold standard" screening test and is regarded as a highly sensitive and specific method for detection of scarring in both native (*26*, *27*) and transplanted kidneys (*28*). Because transient renal parenchymal abnormalities are occasionally seen on 99mTc-DMSA SPECT scan after an episode of acute pyelonephritis, all scans were performed a minimum of 3 months after the last positive urine culture.

Scans were performed using standard technique. Briefly, 75 MBq of 99mTc-DMSA was injected intravenously and imaging performed at 3 hr using a two-headed gamma camera fitted with a high-resolution parallel hole collimator. Data was acquired in a 128×128 W matrix. There were 60 stops of 15 seconds per head so that the total examination time was 15 min. Tomographic slices were reconstructed using a ramp backprojection filter followed by a count-optimized Metz smoothing filter. Images were then reoriented into three orthogonal planes based on planes through the renal hilum and along the longest axis of the kidney. Tomographic data was displayed both as these orthogonal slices and as a three-dimensional (3D) surface volume rendered display (using a cutoff at 45% of maximum pixel counts). The images were reported by two experienced nuclear medicine physicians (A.J.H. and J.R.B.) and were graded into four categories: 1) no focal defects; 2) one focal defect consistent with scarring; 3) two focal defects; and 4) more than two defects. The nature and site of any cortical defect was noted for all patients.

We compared the 99mTc-DMSA SPECT images obtained from patients with a history of UTIs with those of a cohort of renal transplant recipients who had no history of recurrent UTIs in order to determine the utility of the test for detection of scarring due to infection as opposed to noninfective causes. Those in the comparator group had either biopsy-proven chronic allograft nephropathy (CAN; n=11) or angiogram-proven occlusion of a second renal artery (n=8). Although it would have been useful for our purposes to know whether this group had evidence of VUR, none had undergone MCUG examination, as at the time of investigation they had no clinical indication to have this done.

Micturating Cystourethrography

MCUG was performed by standard technique. Briefly, the patient was asked to lie supine on an examination table and a medium size Foley catheter (14–16 French) was inserted using an aseptic technique and any residual urine drained. Radiological contrast medium (Urografin 150) warmed to body temperature was infused through the catheter with the bottle suspended 1 m above the fluoroscopy table. The patient was intermittently screened to look for reflux or any other bladder abnormalities and "spot" films were taken if any abnormality was seen. When the patient's bladder was uncomfortably full, radiographs were taken in the anteroposterior (AP) and oblique projections. Oblique radiographs were obtained during micturition to demonstrate any vesicoureteric reflux. An AP film, to include the transplant kidney, was taken after micturition to assess the presence of contrast medium within the collecting system. The degree of reflux was graded according to the classification of the International Reflux Study Group (*22*). This ranges from grade 1 (reflux into a dilated ureter) up to grade 5 (reflux into a dilated renal pelvis with contrast in the calyces accompanied by tortuosity of the ureters).

Parameters of Graft Function

Values for serum creatinine, creatinine clearance, and 24-hour urine protein excretion, measured on the date that the 99mTc-DMSA SPECT study was performed, were obtained for all patients. All cases were followed until December 1, 2004 to ensure long-term follow up of graft outcomes. Complete follow-up data was available for 31 of 32 patients. One patient with stable graft function transferred out-of-area and was lost to further follow-up 11 years posttransplantation.

Statistical Analysis

Normally distributed datasets were expressed as mean and standard error of the mean. Skewed datasets were expressed as the median and interquartile range and analyzed using nonparametric tests. Prism 3.0 software (GraphPad Software Inc., San Diego, CA) was used to perform the statistical analysis. Chi-square test and Mann Whitney *U* were used for analysis of nonparametric data as appropriate. Graft survival, censored for patient death, was estimated using the Kaplan-Meier method. Curve comparisons were by log-rank test. A P value <0.05 was considered to indicate statistical significance and all tests were two-tailed.

RESULTS

Baseline clinical characteristics of the 32 patients with late recurrent UTIs are outlined in Table 1. Mean patient age at the time of 99mTc-DMSA SPECT imaging was 46 years

TABLE 1. Clinical characteristics of patients with recurrent urinary tract infections (n=32)

Characteristic	Mean (range) or n
Age (years)	46 (22–76)
Male:female ratio	0.14
Primary diagnosis	
Reflux nephropathy	6
Adult polycystic kidney disease	5
Chronic glomerulonephritis	9
Dysplastic kidneys	4
Diabetic nephropathy	1
Hypertension	1
Unknown	6
Reflux on MCUG	
Yes	15
Grade 1	0
Grade 2	3
Grade 3	9
Grade 4	3
No	17
Transplant biopsy[a]	
Yes	17
Chronic allograft nephopathy	5
Rejection	5
Scarring	3
Ciclosporin toxicity	2
Acute tubular necrosis	1
Transplant glomerulopathy	1
No	15

[a] Principal diagnosis from the last transplant biopsy performed before the DMSA scan.

TABLE 2. Comparison of 99m Tc-DMSA SPECT findings in renal allograft recipients with and without a history of recurrent urinary tract infection.

	Recurrent UTIs (%)		Controls (%)	
	Reflux	No reflux	CAN	Vascular occlusion
N	15	17	11	8
No scars	2 (13)	6 (33)	8 (73)	0 (0)
One focal defect	5 (33)	3 (18)	3 (27)	0 (0)
Two focal defects	2 (13)	3 (18)	0 (0)	0 (0)
>Two focal defects	6 (40)	5 (29)	0 (0)	0 (0)
Any focal defect	13 (87)	11 (65)	3 (27)	0 (0)
Segmental defect	0 (0)	0 (0)	0 (0)	8 (100)

(range 22–76 years). The majority were female (28 of 32; 87.5%). The first episode of UTI in the "late" posttransplantation period occurred at a median of 24 months (range 7–108 months). All patients had a minimum of three documented UTIs with a median of six UTIs per patient. For the majority of patients, UTIs were a mixture of relapsing and new infections. Fourteen patients studied had a prior history of symptomatic graft pyelonephritis (typically the combination of fever, graft tenderness, and/or graft dysfunction in the presence of pyuria and a positive urine culture). Seventeen patients had a transplant biopsy performed at some point after transplantation. Findings at biopsy included rejection, acute tubular necrosis, chronic allograft nephropathy, ciclosporin toxicity, transplant glomerulopathy, and extensive scarring with sclerosed glomeruli (Table 1). Median follow-up was 15 years (range 3.8–28.5 years).

Twenty-four patients (75%) were found to have focal renal cortical defects on the 99mTc-DMSA SPECT scan, a pattern typical of scarring due to infection (*29*). Fifteen patients (47%) had evidence of reflux into the graft on MCUG (Table 1). The majority of those with reflux (13 of 15; 87%) had focal cortical defects on 99mTc-DMSA SPECT scan. There was, however, no significant correlation between the number of scars and the degree of reflux although there was a trend towards multiple scars in those patients with more severe reflux (grade 3 or 4). Another noteworthy finding was that scars were seen in almost two-thirds of those patients with a history of UTIs but *without* evidence of vesicoureteric reflux on MCUG (11 of 17; 65%). A history of previous graft pyelonephritis was a significant risk factor for scarring; twelve of 14 of such patients (86%) had focal defects on 99mTc-DMSA SPECT. We did not see a correlation between number of infection episodes and scarring. This may be due to the small numbers and possible confounding by the setting of a threshold of at least three UTIs for inclusion in our study.

Table 2 illustrates the pattern of defects seen on 99mTc-DMSA SPECT scan in the various patient groups. Those with recurrent UTIs typically had one or more focal cortical defects on the scan (Fig. 1A). By contrast, patients with chronic allograft nephropathy typically had an irregular cortical surface (Fig. 1B) with the exception of three patients (3 of 11; 27%) who had unexpected solitary focal defects for which we have no clear explanation. It is conceivable, given the site of these defects (upper pole in each case), that these scars may have resulted from a previous renal transplant biopsy. No patient in this group had multiple defects. In the cohort of patients whose grafts had been scarred by vascular occlusion (e.g., due to loss of a polar artery), the characteristic appearance was of a large segmental defect (Fig. 1C). In this latter group, all defects were consistent with the size of the affected vessel, except in one patient in whom the size of the defect was smaller than expected.

With regard to parameters of graft function (see Fig. 2) levels of proteinuria (measured at the time the imaging studies were performed) were not increased in patients with scars compared with those without scars (0.17 g/24 hrs vs. 0.24 g/24 hrs respectively; $P=0.39$ Mann Whitney U test). Values for serum creatinine obtained at the time of 99mTc-DMSA SPECT scanning were not significantly different for patients with renal scars (132 μmol/L; interquartile range [IQR] 106–185) compared with those without scars (141 μmol/L; IQR 91–200; $P=0.62$ Mann Whitney U test). Creatinine clearance values were also not significantly different (53 mL/min; IQR 38.3–78.6 and 52.7 mL/min; IQR 27.3–86.1, respectively; $P=0.87$ Mann Whitney U test). Interestingly, the presence of scars did not appear to predict decreased graft survival (see

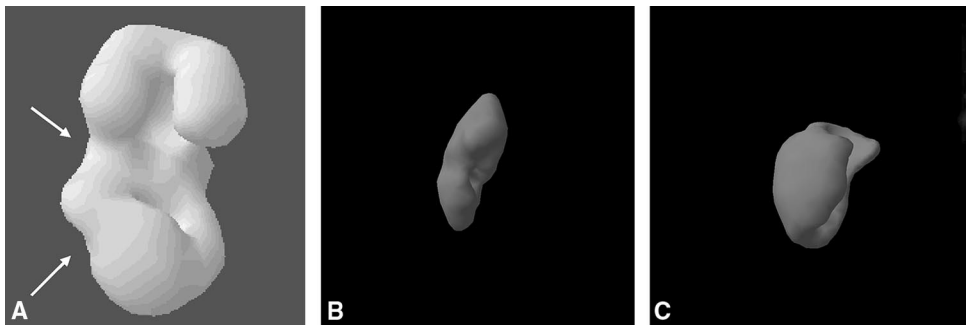

FIGURE 1. 99mTc-DMSA SPECT scans showing: (A) focal cortical defects (arrowed) consistent with scarring in a patient with late recurrent urinary tract infections; (B) cortical irregularity in a patient with chronic allograft nephropathy; and (C) an upper pole segmental defect in a patient with occlusion of a polar artery.

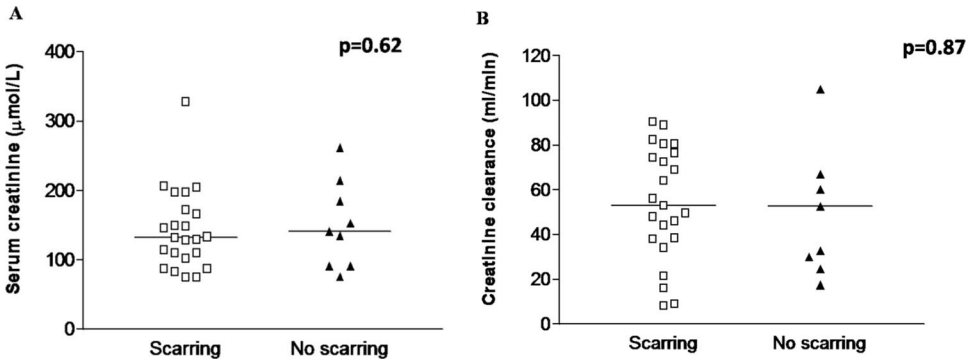

FIGURE 2. Scattergrams comparing median serum creatinine values (A) and creatinine clearance (B) in patients with and without renal scars on 99m Tc-DMSA SPECT scan.

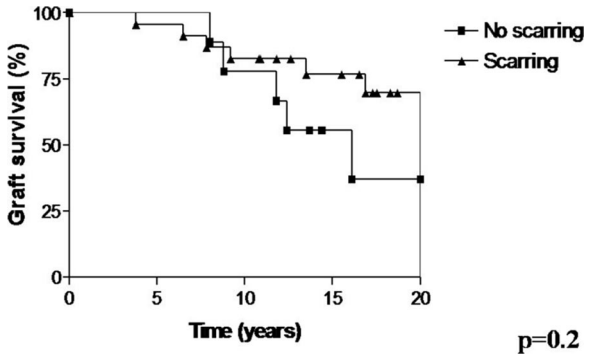

FIGURE 3. Graft outcome in patients with late recurrent urinary tract infections. Kaplan-Meier survival curves showing graft survival in patients with and without evidence of allograft scarring on 99m Tc-DMSA SPECT. Curve comparison was by log-rank test.

Figure 3). This may be the result of selection bias (by definition grafts had to have survived for at least 18 months for inclusion in the study) or may reflect the efficacy of a regimen of prophylactic antibiotic treatment (low-dose nocturnal antibiotic prophylaxis) combined with a routine of regular surveillance urine cultures and prompt treatment of infection, which was instituted for this group of patients.

DISCUSSION

Focal defects consistent with scarring due to infection were seen in the majority of patients with recurrent UTIs, irrespective of the presence of vesicoureteric reflux. This mirrors data from the pediatric literature, where it has been similarly suggested that VUR is not a prerequisite for the development of parenchymal renal infection and subsequent scarring (*30*). A total of 50% of those with scars had had an episode of symptomatic graft pyelonephritis but an equal number had only ever had asymptomatic bacteriuria. VUR was a feature in almost half of patients with recurrent UTIs and patients with VUR were more prone to scarring than those without. Although pyelonephritis and reflux were more frequently associated with scarring, neither was a prerequisite for the development of scars.

The female preponderance (7:1) seen in our cohort is striking and likely reflects the general increased susceptibility of women to UTI; the male:female ratio seen in this transplant cohort mirrors the pattern of urinary tract infection seen in the general adult population (*31*).

One potential confounding factor that should be addressed in our analysis is the significant number of patients (24 of 56) with a history of recurrent UTIs who declined further investigation. Considering this further, if we were to postulate that all in this group were in fact free of scars, the overall rate of scarring associated with recurrent UTIs falls to 43%. Nevertheless, even this figure remains substantially higher than the 27% rate of scarring seen in the group with CAN, suggesting that the association between recurrent UTIs and the development of allograft scarring is likely to be robust.

The high rate of graft scarring seen in this study is somewhat unexpected. Given that scarring of native kidneys as a result of VUR/UTI is rare beyond the age of 5 years (*9*), it seems surprising that renal allografts, all of which were from

adult donors, should be susceptible to scarring. It is possible that asymptomatic upper tract involvement is a frequent occurrence in renal allograft recipients and that immunosuppression makes these kidneys more vulnerable to damage.

CONCLUSIONS

In renal allograft recipients with a history of late UTIs, renal scarring is a frequent finding and the pattern of scarring seen (multiple focal cortical defects) suggests a direct causative link. Scarring can occur even in asymptomatic patients without evidence of VUR. The presence of renal scarring was not associated with inferior graft survival in this series. This may reflect selection bias or the impact of more intensive surveillance and use of prophylactic antibiotic therapy for this group of patients.

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