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FREQUENCY OF RECURRENT LUPUS NEPHRITIS AMONG NINETY-SEVEN RENAL TRANSPLANT PATIENTS DURING THE CYCLOSPORINE ERA

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Objective. **To determine the frequency of recurrent lupus nephritis (LN) in patients with systemic lupus erythematosus (SLE) who underwent renal transplantation.**

Methods. **We reviewed the posttransplant clinical course and renal biopsy results in 97 consecutive SLE patients who underwent a total of 106 renal transplantation procedures at our center from January 1984 to September 1996.**

Results. **There were 81 female and 16 male patients, with a mean age of 35 years. Mean duration of dialysis prior to transplantation was 33.5 months; 9 patients were never dialyzed. In all patients, the disease was clinically and serologically quiescent at the time of transplantation. The mean posttransplantation followup period was 62.6 months. Patients underwent a total of 143 posttransplant biopsies. Nine patients had pathologic evidence of recurrent LN. Six of the patients with recurrence had cadaveric grafts, 2 had living-related grafts, and 1 had a living-unrelated graft. Recurrence occurred an average of 3.1 years after transplantation; the longest interval was 9.3 years and the shortest, 5 days. Histopathologic diagnoses on recurrence included diffuse proliferative glomerulonephritis, focal proliferative glomerulonephritis, membranous glomerulonephritis, and mesangial glomerulonephritis. In 4 patients, recurrent LN contributed to graft loss. Three of the patients with recurrence had serologic evidence of active lupus, but only 1 had symptoms of active lupus (arthritis). Three patients who lost their grafts secondary to recurrent LN underwent second renal transplantation procedures and had functioning grafts at 7, 30, and 35 months, respectively.**

Conclusion. **In the largest single medical center series of renal transplant patients with SLE, recurrent LN was more common than reported in the literature, but was not always associated with allograft loss. Recurrent LN was often present in the absence of clinical and serologic evidence of active SLE.**

In the early days of renal transplantation—the late 1960s through the mid-1970s—physicians were reluctant to offer renal transplantation to patients with systemic lupus erythematosus (SLE) because it was feared that lupus nephritis (LN) would recur quickly and destroy the allograft (1–3). Over the past 2 decades, however, the experience with renal transplantation in SLE has demonstrated that many SLE patients with end-stage renal disease are excellent transplant candidates (4–9). Despite the more widespread use of renal transplantation in SLE, the frequency of recurrent LN in the allograft has not been well studied. Two literature reviews of disease recurrence have estimated the incidence of recurrent LN to be <1% (10,11). However, because of the lack of studies specifically designed to address the question of recurrence frequency, this estimate was based primarily on case reports of recurrent LN.

Previous estimates of recurrence frequency may have been low, for several reasons. First, the number of SLE patients who receive renal transplants at most centers is small. The median number of SLE patients reported in all studies from individual transplantation centers in the past 2 decades is 16 (12). The largest single-center series published to date involved a cohort of 69 SLE patients who underwent transplantations over

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a period of 23 years in conjunction with a variety of immunosuppressive regimens (6). Thus, the relative inexperience at most medical centers with renal transplantation in SLE precludes firm conclusions about the frequency of recurrence. Second, recurrences of LN may be underreported, because the frequency of recurrence has not been the primary research question in most outcome studies (5,6,9,13–22). The few multicenter studies of renal transplantation in SLE have focused on outcomes (i.e., allograft success or failure) and failed to address the question of recurrence frequency (4,7,8,23,24). Third, patients with allograft dysfunction are often treated empirically for rejection, without confirmatory biopsies. In the absence of a transplant biopsy, recurrent LN may be overlooked and treated as an episode of rejection (10).

The introduction of cyclosporine as a novel immunosuppressive agent in the early 1980s marked the beginning of a new era in organ transplantation. Since 1984, cyclosporine (or, more recently, FK506/tacrolimus) has been part of the standard immunosuppressive regimen for renal transplant patients at most medical centers, including ours. We carefully evaluated the frequency of biopsy-proven recurrent LN in patients who underwent renal transplantation at our institution during the cyclosporine era. This cohort comprises the largest group of renal transplant patients with SLE ever reported from a single center (before or after the introduction of cyclosporine). Moreover, this is the first systematic study designed to determine the frequency of recurrent LN.

PATIENTS AND METHODS

All SLE patients who underwent renal transplantation at the University of California, San Francisco (UCSF) between January 1, 1984 and September 1, 1996 were included in the study. Transplant patients with SLE were identified by diagnosis through the Organ Transplantation & Immunogenetics System (OTIS), a computer database of all patients who have received organ transplants at UCSF. We cross-checked the list of patients in OTIS with a list of all UCSF hospital and clinic patients with diagnoses of SLE *and* nephritis. To ensure that we did not fail to include significant numbers of SLE patients whose causes of end-stage renal disease were incorrectly recorded in OTIS, we randomly chose and reviewed the medical records of 125 transplant patients from the same period who had either a non-SLE disease or "unknown" listed as the cause of their end-stage renal disease. These 125 patients represented ~5% of all patients who received renal transplants at our center during the time period covered by the study.

Patients' diagnoses of SLE were confirmed in a rigorous medical records review (as described below). All patients included in the study either met at least 4 of the American College of Rheumatology revised criteria for the diagnosis of SLE (25) or had pretransplant renal biopsy findings consistent with a diagnosis of LN. Pathologic features considered to be consistent with LN (26) included 1) light microscopy findings demonstrating either membranous or proliferative changes in the glomeruli, with or without interstitial nephritis; 2) positive immunofluorescence staining for immunoglobulins (IgG and either IgM or IgA), C3, and C1q; or 3) electron microscopy findings demonstrating either electron-dense deposits in the mesangium or basement membranes, or tubuloreticular inclusion bodies within endothelial cells.

At the time of transplantation, all SLE patients were believed to have clinically and serologically quiescent disease. In general, this meant that, compared with periods of SLE flares, a patient's serum levels of complement and antibodies to double-stranded DNA were relatively normal, and that there was no clinical evidence of active SLE. All of the patients in this study received identical basic posttransplantation immunosuppressive regimens, which consisted of cyclosporine (or, more recently, tacrolimus), azathioprine (or, more recently, mycephenolate), and prednisone. Except for minor variations from year to year, this basic regimen was the same for virtually all types of renal transplant patients at our center during the period of study.

We ascertained the transplantation outcomes of all SLE patients who received renal transplants during the time period of the study, including the current status of each allograft, the cause of each allograft loss, and the cause of every death. Complete followup, defined as the time period from transplantation until September 1, 1996 or patient death, was achieved through several approaches: 1) review of patients' pretransplantation evaluations, including records from referring physicians; 2) review of hospital charts, containing details of the transplant hospitalization as well as subsequent hospitalizations; 3) review of transplant clinic charts, containing records of longitudinal followup visits after transplantation; 4) review of pertinent outside medical records; 5) inquiries to the United Organ Sharing network about missing patient data; and 6) telephone interviews with patients or surviving family members.

The indications for posttransplant renal biopsy at UCSF included the following unexplained abnormalities: 1) hematuria or cellular casts in the urine sediment; 2) significant proteinuria; or 3) the development of azotemia relative to the baseline status of a patient's transplanted kidney. Because more than 95% of all patients who undergo transplantation at our center receive longitudinal followup in the UCSF Transplant Clinic, most posttransplant renal biopsies are performed at UCSF.

For every SLE patient who underwent transplantation at UCSF during the period of study, we reviewed the transplant specimens that were available from renal biopsies performed at UCSF. We also reviewed the original reports on biopsy specimens that had been obtained at UCSF but were not available for review (6% of all biopsies). In addition, we assessed the pathology reports on the few biopsy specimens that were obtained from centers other than UCSF. If the outside reports suggested a recurrence of LN, we obtained and reviewed the original slides. We screened the biopsy samples by reviewing the light microscopy findings. If a light micro-

Table 1. Specific pathologic features examined in renal biopsy samples obtained from transplant patients with systemic lupus erythematosus

Pathologic study	Feature
Light microscopy	Glomerular hypercellularity; loop thickening; crescents; hyaline thrombi; necrotizing lesions; hypertensive changes; interstitial nephritis/fibrosis; tubular atrophy; glomerulosclerosis
Immunofluorescence	Glomerular deposition of IgG, IgM, IgA, C3, and C1q
Electron microscopy	Tubuloreticular inclusions; electron-dense deposits in specific regions (mesangium, subendothelial space, subepithelial space, tubular basement membrane)

graph revealed proliferative or membranous changes consistent with SLE, we reviewed the immunofluorescence and electron microscopy findings for that biopsy sample. When diagnostic clarification was needed, we performed special stains on the biopsy specimen. Using a standardized data collection form, we noted the presence or absence of specific pathologic features, as listed in Table 1.

After reviewing all of the available clinical and pathologic data, we classified the results of each biopsy as demonstrating either recurrent LN or another pathologic diagnosis (e.g., acute rejection, chronic allograft nephropathy/rejection, cyclosporine toxicity, or thrombotic microangiopathy). The cases of recurrent LN were classified further according to the World Health Organization (WHO) classification scheme (27).

In addition to information about allograft status, cause of allograft loss, and cause of death, we collected data on covariates that were possibly associated with recurrence or poor transplantation outcome. These covariates are listed in Table 2. We examined the associations of these covariates with recurrent LN using *t*-tests for continuous variables and chi-square tests for categorical variables. Significance levels were adjusted for the number of comparisons using the Bonferroni method (28). *P* values less than or equal to 0.005 were considered to be statistically significant.

Table 2. Clinical data collected on all transplant patients with systemic lupus erythematosus (SLE)

Pretransplant
Demographic information (age, race, sex)
Type of allograft received (cadaveric, living-related, or living-unrelated)
Smoking history
Treatment for nonrenal SLE manifestations within a year preceding transplantation
Donor age
Number of mismatches at the HLA-A, HLA-B, and HLA-DR loci
Levels of panel-reactive antibodies
Presence of antilymphocyte antibodies
Number of pregnancies prior to transplantation
Number of blood transfusions prior to transplantation
Posttransplant
Occurrence of delayed graft function
Posttransplant blood pressure measurements
Posttransplant renal biopsy results
Current allograft status
Cause of allograft loss
Cause of death

Table 3. Primary pathologic diagnoses in posttransplant renal allograft biopsies

Pathologic diagnosis	No. of allografts
Acute rejection	66
Chronic allograft nephropathy/rejection	37
Recurrent lupus nephritis	12*
Cyclosporine toxicity	7
Acute tubular necrosis	4
Focal cortical ischemia	1
Normal	9
Nonspecific changes	6
Biopsy insufficient for diagnosis	1
Total	143

* Patients 2, 3, and 5 each had 2 biopsies of the same allograft that demonstrated recurrence of lupus nephritis.

RESULTS

Ninety-nine transplant patients with end-stage renal disease secondary to SLE were identified through the computer search described above. Three patients were excluded because review of their records failed to confirm the diagnosis of SLE and suggested other diagnoses. The causes of end-stage renal disease in these 3 patients were IgA nephropathy, hemolytic-uremic syndrome, and non-SLE "familial nephropathy." Among the 125 cases identified as non-SLE or "unknown," we found 1 patient whose cause of end-stage renal disease was actually SLE, and included this patient in the SLE group. Thus, 97 patients with SLE (recipients of a total of 106 renal transplants at our center) comprised the study group. Three patients received their first transplants at other medical centers. These procedures were not included in our study. The 106 transplantation procedures included 94 first transplants and 12 second transplants. Eighty-one (83.5%) of the patients were female and 16 (16.5%) were male. The average age of the patients was 35 years (range 15–61 years). The average duration of followup on the patients (defined as the time of transplantation until September 1, 1996 or until patient death) was 250.4 weeks.

Seventy-one of the 97 patients who received kidney transplants underwent a total of 143 biopsies. The biopsy results are given in Table 3. During the followup period, biopsy specimens from 9 different patients demonstrated recurrent LN, for a recurrence frequency of 8.5% (9 of 106 transplantation procedures). In 8 of the 9 cases of recurrence, the reviewing pathologists (CLM and JLO) agreed with the original patho-

Table 4. Pretransplant clinical characteristics of the patients by recurrence or nonrecurrence of lupus nephritis*

Characteristic	Recurrence (n = 9)	Nonrecurrence (n = 91)†
Age, years	29.9 ± 7.9	35.1 ± 9.7
No. (%) female	8 (89)	76 (84)
No. (%) white	5 (56)	35 (38)
Treatment within 1 year for active (nonrenal) SLE, no. (%)	2 (22)	11 (12)
Length of dialysis, weeks	120 ± 156	135 ± 140
No. of HLA mismatches	4.2 ± 1.6	4.1 ± 1.7
Current levels of panel-reactive antibodies‡	1.6 ± 2.0	12.9 ± 21
No. of rejection episodes§	0.67 ± 1.0	0.62 ± 0.83

* Except where otherwise indicated, values are the mean ± SD. Statistical *t*-tests were performed for comparison of continuous variables, and chi-square tests for categorical variables. Significance levels were adjusted for the number of comparisons by the method of Bonferroni (28). SLE = systemic lupus erythematosus.
† Three patients (3, 4, and 8) were in both the recurrence and nonrecurrence groups.
‡ Determination of panel-reactive antibodies is a standard test performed at the time of transplantation that quantifies the number of preformed recipient antibodies reactive against a group of lymphocytes whose antigens are representative of the population pool of HLA antigens. Higher current levels were associated with a lower risk of recurrence ($P = 0.001$).
§ Defined as biopsy-proven acute rejection.

logic readings. In the ninth case (patient 9), special staining performed by us after we reviewed the original light micrograph revealed a diagnosis of membranous LN. Eight patients had recurrent LN following their first renal transplantation. One patient (patient 8), whose first allograft failed at postoperative day 14 because of a thrombotic microangiopathy associated with antiphospholipid antibodies, experienced a recurrence of LN in her second allograft. The pretransplant clinical features of the SLE patients who had recurrences were compared with those of patients in the nonrecurrence group (Table 4).

The mean followup times until graft loss for the recurrence and nonrecurrence groups were virtually identical (166.6 weeks for the former versus 165.0 weeks for the latter). The patients with recurrence were similar to those in the nonrecurrence group in terms of sex and race distributions, but were slightly younger at the time of transplantation (29.9 years versus 35.1 years; $P = 0.12$). The percentage of patients with cadaveric renal transplants (66.7% versus 72.4%) and the mean number of mismatches at the 6 HLA loci (4.2 versus 4.1) were comparable in the 2 groups. The mean number of posttransplantation rejection episodes per patient was also similar between the 2 groups (0.67 versus 0.62).

Because some of the literature on renal transplantation in SLE has suggested that a shorter pretransplantation dialysis period is associated with a greater likelihood of posttransplant disease activity, we examined the relationship between dialysis and recurrent LN. All 9 of the patients with recurrences underwent hemodialysis prior to transplantation (patient 7 also received peritoneal dialysis during her pretransplantation course). In contrast, 9 patients in the nonrecurrence group were never dialyzed before transplantation. The average length (±SD) of pretransplantation dialysis among the patients with recurrence was 120 weeks (±156), compared with 135 weeks (±140) for the nonrecurrence group ($P = 0.89$).

A standard test to determine the current levels of panel-reactive antibodies (PRA) was performed at the

Table 5. Characteristics of the patients with recurrent lupus nephritis*

Patient	Age at transplantation, years	Allograft type	Time to recurrence, weeks	WHO pathologic class	Effect of recurrence on allograft
1	46	CRT	100	II	None
2	37	CRT	156	IV	Allograft loss
3	22	CRT	84	III	None
4	29	LRRT	132	II	Allograft loss†
5	28	CRT	484	IV	Allograft loss
6	32	CRT	5 days	II	None
7	30	LURT	40	Vb	None
8	20	LRRT	111	II	None
9	25	CRT	364	Va	Allograft loss†

* Mean age of the 9 patients was 29.9 years and mean time to recurrence of lupus nephritis was 159.5 weeks. The World Health Organization (WHO) pathologic class (see ref. 27) was defined as follows: II = mesangial glomerulonephritis; III = focal proliferative glomerulonephritis; IV = diffuse proliferative glomerulonephritis; Vb = membranous glomerulonephritis with focal proliferative features; Va = pure membranous glomerulonephritis without proliferative features. CRT = cadaveric renal transplant; LRRT = living-related renal transplant; LURT = living-unrelated renal transplant.
† Loss secondary to both recurrence and chronic rejection.

Table 6. Biopsy findings in the patients with recurrent lupus nephritis*

Patient	Light microscopy	Immunofluorescence	Electron microscopy	Other	WHO class
1	Normal	IgG; IgM; C3	TRI; mesangial DD	None	II
2	Necrotizing lesions; crescents; glomerular hypercellularity; loop thickening; hyaline thrombi	IgG; IgM	Mesangial and subendothelial DD; TRI	HTN changes; IN; TA; occasional GS	IV
3	Glomerular hypercellularity	Not available	Mesangial, subendothelial, and subepithelial DD; TRI	HTN changes; IN; mild TA; focal GS	III
4	Glomerular hypercellularity; loop thickening	Multiple small immune deposits (not specified)	Mesangial DD; TRI; TBM deposits	TA; GS	II
5	Crescents; glomerular hypercellularity; loop thickening	IgG; IgM; IgA; C3	Mesangial, subendothelial, and subepithelial DD; TRI	IN; TA	IV
6	Mild glomerular hypercellularity; mesangial matrix increase	IgG; IgA; C3; C1q	Mesangial DD	IN	II
7	Loop thickening	IgG; IgM; IgA; C3	Mesangial and subepithelial DD	IN; minimal TA; mild GS	Vb
8	Glomerular hypercellularity; mesangial deposits on special stains	Insufficient tissue available	Insufficient tissue available	None	II
9	Loop thickening; subepithelial deposits on special stains	Not performed	Not performed	Mild IN	Va

* See Table 5 for definition of the World Health Organization (WHO) classes. TRI = tubuloreticular inclusion bodies; DD = electron-dense deposits; HTN = hypertensive; IN = interstitial nephritis; TA = tubular atrophy; GS = glomerular sclerosis; TBM = tubular basement membrane.

time of transplantation. This test quantifies the number of preformed recipient antibodies that are reactive against a group of lymphocytes whose antigens are representative of the population pool of HLA antigens. In univariate analyses, the current levels of PRA were found to be inversely associated with the likelihood of recurrent LN ($P = 0.001$). None of the other variables examined were associated with recurrent LN after correction for multiple comparisons.

The posttransplant clinical features of each patient with recurrent LN are shown in Table 5, and the specific pathologic findings for the 9 recurrent LN cases are listed in Table 6. The average time to recurrence was 159.5 weeks. The shortest interval between transplantation and recurrence was 5 days, and the longest, 9.3 years. In the patient with the shortest recurrence interval (patient 6), light microscopy demonstrated increases in the mesangial matrix and cellularity (Figure 1), immunofluorescence revealed positive staining for IgG, IgA, C3, and C1q, and electron microscopy demonstrated electron-dense deposits in the mesangium. We classified this recurrence as mesangial LN (WHO class II). The patient with the longest interval between transplantation and diagnosis of recurrence (patient 5) had intermittent arthralgias, hypocomplementemia, and elevated titers of anti–double-stranded DNA antibodies for several years after transplantation. When she developed nephrotic-range proteinuria and renal dysfunction, a renal biopsy was performed. The histopathologic findings of the biopsy were consistent with diffuse proliferative LN (WHO class IV) (Figures 2A and B).

In the 9 patients with recurrent LN, pre- and

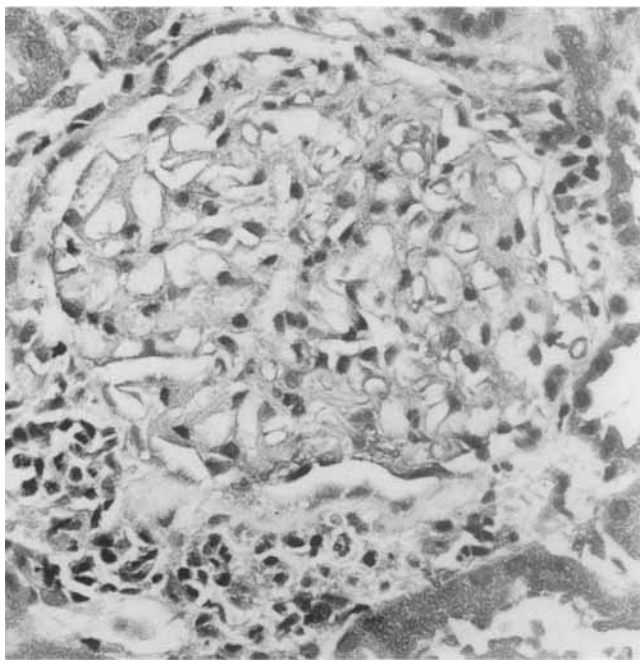


Figure 1. Light micrograph of a glomerulus from a patient with systemic lupus erythematosus and recurrent lupus nephritis (patient 6), showing mild mesangial matrix increase and hypercellularity. Also note the presence of interstitial nephritis below the glomerulus (hematoxylin and eosin stained; original magnification × 420).

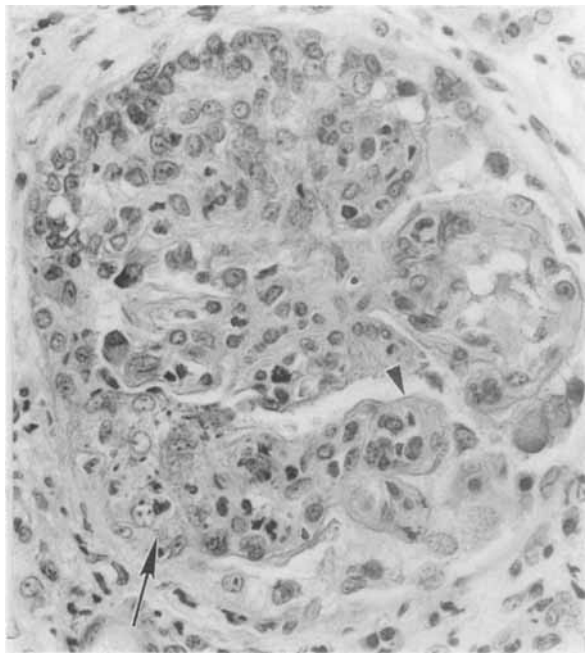
posttransplantation parameters of SLE activity (clinical and serologic) were determined, as shown in Table 7, along with the presenting features of their recurrence. Except for patient 5 (described above), no patient had overtly active SLE (defined as the presence of clinical findings *and* serologic abnormalities) at the time of recurrence. However, 3 patients had serologic evidence of active disease *without* clinical manifestations of SLE (aside from renal dysfunction). Information on serologic parameters at recurrence was not available for 3 patients.

There was 1 death in the recurrence group, compared with 19 in the nonrecurrence group (12.5% versus 19.4%; $P = 0.99$). A higher percentage of patients with recurrence lost their grafts (66.7% versus 48.0%; $P = 0.18$). Six patients with recurrent LN ultimately lost their grafts, and LN clearly contributed to the allograft loss in 4 of the patients. In 2 patients (patients 2 and 5), both of whom had diffuse proliferative glomerulonephritis, recurrent LN was the direct cause of allograft failure. In 2 others (patients 4 and 9), recurrent LN and chronic rejection both contributed to loss of the allograft. Overall, 52 (49.1%) of the 106 renal transplantation procedures failed during the followup period. Thus, recurrent LN played a role in 7.7% (4 of 52) of the total number of allograft failures. In comparison, acute and chronic rejection accounted for 9 (17.3%) and 28 (53.8%) of the allograft failures, respectively. Complications of the antiphospholipid antibody syndrome resulted in 8 failures (15.4%).

To date, 3 patients with recurrent LN have experienced neither allograft loss nor significant impairment of allograft function. However, because these 3 patients have only been followed up for 6, 47, and 100 weeks, respectively, since their diagnoses of recurrence, it is premature to draw conclusions about the effect of recurrent LN on their transplantation outcomes. Three patients who had recurrence and allograft loss (patients 2, 4, and 9) have received second renal transplants, and all continue to have functioning allografts at 28, 132, and 152 weeks, respectively. A fourth patient (patient 5) continues to have clinically and serologically active SLE, and remains on the transplantation waiting list pending the quiescence of her disease.

DISCUSSION

We reviewed the experience with 97 SLE patients who underwent renal transplantation at our center from 1984 to 1996, after the introduction of cyclosporine as an immunosuppressive agent. We determined that the frequency of recurrence of LN during the period of followup (mean 250.4 weeks) was 8.5%. Recurrent LN played a role in 7.7% of all allograft losses in the SLE patients during the time period of study. This study of



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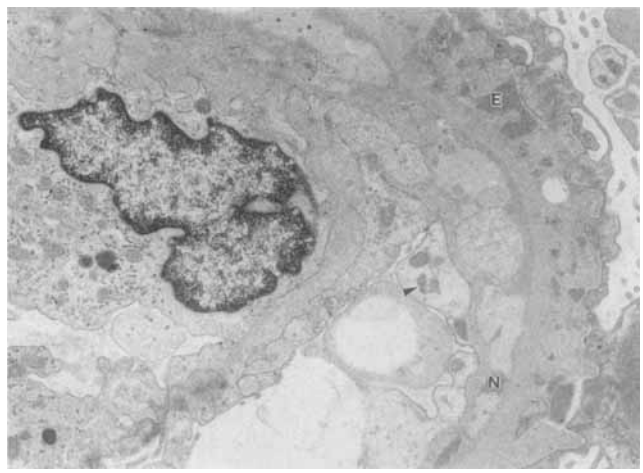

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Figure 2. A, Light micrograph of a glomerulus from a patient with systemic lupus erythematosus and recurrent lupus nephritis (patient 5), showing proliferative lupus nephritis characterized by marked hypercellularity, increased mesangial matrix, thickened capillary loops (**arrowhead**), and a segmental necrotizing lesion (**arrow**) (hematoxylin and eosin stained; original magnification × 380). **B,** Electron micrograph of a portion of a capillary loop showing subepithelial (**E**) and subendothelial (**N**) deposits. Also note the reduplication of the basement membrane ("double contour") to the left of the subendothelial deposits. The endothelial cells are swollen and contain a tubuloreticular inclusion (**arrowhead**) (uranyl acetate and lead citrate stained; original magnification × 12,000).

Table 7. Pre- and posttransplant serologic results and clinical presentation of recurrence of lupus nephritis in patients with systemic lupus erythematosus (SLE)*

Patient	Pretransplant serologic findings	Serologic findings at recurrence	Renal signs of recurrence	SLE clinically active at recurrence
1	Normal	Not done	None	No
2	Normal	Normal	Nephrotic syndrome	No
3	Normal	↑ dsDNA	None†	No
4	Normal	↑ dsDNA	None†	No
5	Normal	↑ dsDNA; ↓ complement	Nephrotic syndrome	Yes
6	Normal	dsDNA not done; ↓ C3	Posttransplant allograft slow to function	No
7	Normal	Not determined	Proteinuria (2.25 gm/24 hours)	No
8	Normal	Normal	↑ creatinine	No
9	Normal	Not done	↑ creatinine	No

* Serologic tests included determinaton of antibodies to double-stranded DNA (dsDNA) and serum complement levels within 6 months of transplantation.
† Patient had a decline in renal function attributed to chronic rejection.

recurrent LN following renal transplantation provides the best current information about the frequency of the problem, and is the largest report from any single medical center. Because LN may yet recur in some of the 54 surviving SLE patients who still have functioning allografts, 8.5% should be considered the *minimum* frequency of recurrence for a followup period of this length.

Our findings suggest that the frequency of recurrent LN is higher than that previously reported in the literature. Most estimates of the frequency of recurrence, which are found primarily in case reports, have been on the order of 1–2% (21,29–32). In 2 formal reviews of recurrent original disease (including many diseases known to recur in the allograft), the authors concluded that the incidence of recurrent LN was <1% (10,11). Our review of outcome studies from the past 2 decades revealed that only 13 of the 21 reports of renal transplantation in SLE included comment on either the presence or absence of recurrent LN in the populations studied (12). These 13 studies comprised a total of 331 patients. Among these 331 patients, 7 cases of recurrent LN were reported, thus implying a recurrence frequency of 2.1%. The time to recurrence was not reported in most of these cases. A frequency of 2.1% underestimates the true incidence of recurrence, for several reasons: 1) underreporting is a possibility, because recurrence frequency was not the studies' primary research question; 2) misdiagnosis of recurrence as rejection may have occurred, because of failure to perform renal biopsies; and 3) the followup period was insufficient to detect late recurrences, which took place in patients at 7 and 9 years after transplantation in our series and also have been reported up to 8 years following transplantation in other studies (5).

Although recurrent LN appears to be more common than previously recognized, it has been a relatively unusual cause of allograft failure in our experience. The precise etiology of allograft loss is sometimes difficult to determine, but 2 patients in our study clearly experienced allograft failures as a direct result of recurrent LN, and recurrence contributed to allograft loss in 2 others. Thus, 4 (3.8%) of the 106 transplantation procedures failed, at least in part, because of recurrent disease in the allograft. (In general, recurrences of LN were treated with increased doses of prednisone and other transplantation immunosuppressive agents, rather than with cyclophosphamide or other medications typically used to treat LN.) Compared with other causes of allograft loss in our patients (e.g., rejection), the number of patients who lost allografts secondary to recurrence was relatively small. In fact, in our study, more patients lost their grafts secondary to complications of the antiphospholipid antibody syndrome (n = 8) than to recurrent LN (n = 4).

Despite careful examination of the pre- and posttransplantation characteristics of the SLE patients, there were few distinguishing features between the recurrence and nonrecurrence groups. The 2 groups were strikingly similar in terms of demographic characteristics, pretransplant disease activity and immunosuppression, HLA matching, and number of acute rejection episodes. Thus, a priori prediction of patients at risk for recurrence remains a difficult task. Surprisingly, higher current PRA levels were associated with a lower risk of recurrent LN. This finding is counterintuitive; because

of the increased immune reactivity associated with SLE, we expected to find the opposite relationship between PRA levels and recurrent LN. Thus, this finding should be confirmed in other series of transplant patients with SLE. Our experience supports the conclusion of other investigators regarding the poor correlation between clinical and serologic measures of disease activity and the likelihood of recurrent LN (29). Only 1 of our patients had both clinical and serologic evidence of active disease at the time of recurrence.

Patient 6 had the shortest interval on record between transplantation and recurrent LN. We considered alternative explanations for her apparent recurrence, including the existence of SLE in the donor kidney. The donor for patient 6, however, was a 16-year-old male with no known underlying illnesses, who died of accidental causes, making subclinical SLE highly unlikely. Because the light microscopy, immunofluorescence, and electron micrograph findings from the allograft biopsy samples were all consistent with SLE nephritis, we concluded that patient 6 had recurrent LN.

Because of the longstanding view of SLE as the prototypic human immune complex disease, it is perhaps surprising that LN does not recur with a higher frequency than our study suggests. Several other immunologically mediated causes of end-stage renal disease, such as antiglomerular basement membrane disease and cryoglobulinemia, are reported to recur with much higher frequencies in renal allografts (30% and 50% of transplant patients, respectively [11]). There are 2 likely explanations for the comparatively low recurrence rate among transplant patients with SLE. First, the natural history of the disease in many patients may involve a course of either months or years of disease activity before quiescence occurs. This has been reported not only in SLE patients with end-stage renal disease (33), but also in some patients without renal involvement (34). Second, as a criterion for transplantation at most medical centers, SLE patients must have no clinical or serologic evidence of active disease. Thus, SLE patients who are approved for transplantation may represent a population at low risk for future disease flares.

Our study had several limitations. First, the gold standard approach to studying the frequency of recurrence of LN in SLE patients would be to perform "surveillance" transplant biopsies on all patients at regular (e.g., 1-year) intervals. Because of the morbidity associated with such a study, however, this is not ethically feasible. However, since there was a low threshold for performing biopsies at our institution, 74% of the SLE patients in our study underwent at least 1 transplant biopsy at some point in their disease course. The patients who did not undergo biopsies either had no clinical indication for a biopsy (because their grafts were functioning well) or died from causes unlikely to be related to recurrent LN (e.g., infection or cardiac arrest). Second, because we required biopsy confirmation in all cases of recurrence, it is conceivable that we missed some subclinical cases of recurrence. In our thorough medical records review and patient followup, however, we found no cases of "presumed" (unbiopsied) cases of recurrent LN. Furthermore, the close contact between patients, their local physicians, and the UCSF Transplant Clinic makes it unlikely that recurrences diagnosed elsewhere were not reported to us. We believe that all cases of clinically significant recurrences were detected in our patient population. Finally, retrospective evaluation of pretransplantation SLE activity tends to be difficult, and our use of treatment for active disease within 1 year before transplantation was only a crude measure of disease activity. However, the transplant physicians at our center routinely delay transplantation in SLE patients until the disease has been quiescent, in terms of clinical symptoms and serologic measures, for at least 6 months.

In summary, we carefully reviewed the posttransplantation clinical courses and renal biopsy results in 97 patients with SLE who received transplants at our center since 1984. During an average followup of 250.4 weeks, recurrent LN was observed in 9 patients, or 8.5% of all renal transplantation procedures performed in SLE patients during the period of the study. Although LN recurs more frequently than previously believed, the frequency of recurrence is still far less than was predicted in the early days of renal transplantation (1–3). Furthermore, recurrent LN is a relatively rare cause of allograft loss. Concern about recurrence of LN should not preclude renal transplantation in patients with end-stage renal disease secondary to SLE. Further study of renal transplantation in SLE may lead to improved recognition of risk factors for disease recurrence in the allograft and may contribute to improvement of the overall transplantation outcome.

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