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ORIGINAL ARTICLE

Impact of recurrent lupus nephritis on lupus kidney transplantation

A 20-year single center experience

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Abstract This study was conducted to delineate the frequency of recurrent lupus nephritis in a Chinese kidney transplant cohort and to estimate its impact on long-term transplant outcomes. A total of 32 lupus transplant patients were enrolled in this study, and the medical records were retrospectively reviewed. Patients with unexplained graft abnormalities were subjected to allograft biopsy. Recurrent lupus nephritis was diagnosed by light microscopy, immunofluorescence, and electron microscopy. In addition, to determine the clinical manifestations of recurrent lupus GN in these patients, serum original systemic lupus erythematosus disease activity index (SLEDAI) scores while undergoing allograft biopsy were evaluated. In total, six out of 32 patients (18.8%; mean age, 40.5±9.1 years) were diagnosed as having recurrent lupus nephritis and the mean time at diagnosis was 5.1±4.9 years post-transplantation. According to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 criteria, three of the six cases (50%) were defined as class I, one was class II, one was class IV, and one was class III + V. The graft and patient survival rates of recurrent lupus nephritis (n=6) were not different from those of patients with other diagnostic entities. Although recurrent lupus nephritis was not uncommon, it did not appear to have a strong negative impact on long-term outcome in Chinese kidney transplant patients. The recurrence was potentially treatable and should not be precluded for receiving transplantation.

Keywords Chinese population · Chronic rejection · Histological transformation · Original SLEDAI score · Recurrent lupus nephritis

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Introduction

Renal transplantation has been successfully performed in systemic lupus erythematous (SLE) patients with end-stage renal disease (ESRD) since 1959 [1].

Although a comparable survival rate has been reported [2–5], the recurrence of lupus nephritis (RLN) remains a concern [6–12] because SLE is a systemic disease with a plethora of auto-antibodies which may be detrimental to the renal allograft [13,14]. With the development of newer more

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potent immunosuppresants, it was believed that the recurrence would become uncommon. However, recent data have shown that the recurrence rate may be higher than previously recognized, ranging from 0% to 30%, and the great variation may be due to the diagnostic criteria used in different reports [13–15]. A complete evaluation of the biopsy specimen including light microscopy, immunofluorescence staining and electron microscopy is suggested to establish the diagnosis [12]. For instance, early recurrence (class I) may have a completely normal appearance under light microscopy but may already display abundant immune complex deposition, which can only be detected under immunofluorescence or electron microscopy examination. However, the clinical significance of recurrent lupus nephritis remains unclear.

Previously, we demonstrated comparable long-term outcomes in SLE kidney transplants and non-SLE kidney transplants in a Chinese cohort [16].

In this report, we extend our scope of observation and attempt to elucidate the status and impact of recurrent lupus nephritis on Chinese renal transplant recipients.

Patients and methods

Between 1984 and 2009, a total of 1,050 renal transplant recipients were followed up in our hospital. Of these patients, 32 patients had lupus nephritis as the primary disease of renal failure. The diagnosis of SLE was made according to the American College of Rheumatology, which requires that patients meet at least four of the revised criteria. Hospital and clinical charts were retrospectively reviewed. Documented information included demographics, such as age, gender, and race, donor source (cadaver or living), HLA-antigen compatibility, histopathologic diagnosis of the native kidney (by WHO classification), and renal replacement therapy. The immunosuppressive regimen and laboratory data, including HLA matching, panel reactive antibody (PRA), virus serological markers (e.g., hepatitis virus B and C), and urine protein and sediment, were also recorded. All of the patients were followed up monthly in our outpatient department for their graft function and biochemical analysis, urinalysis and complete blood counts. All lupus transplant patients visited our outpatient department once per month. Patients were closely monitored and examined for renal function at regular intervals for the following: glomerular filtration rate (GFR), serum creatinine, 24-h urine protein, urine sediment, anti-double stranded DNA (anti-ds DNA) antibodies, complement levels (C3, C4), antinuclear (ANA) antibodies, etc. Patients were subjected to a graft biopsy if daily proteinuria (DUP) >500 mg with or without active sediments and serum creatinine >0.5 mg/dl. All patients gave informed consent before they underwent the procedure of renal biopsy. The definition of RLN in the grafted kidney in our study was based on the biopsy findings of light microscopy, immune deposits by immunofluorescence, and electron-dense deposits of immune complexes by electron microscopy. Lupus nephritis was classified according to the system of Weening et al. [17] based on the biopsy of a native kidney and was modified here for the transplant situation. The Banff (97) classification was used to determine graft lesions other than recurrent lupus nephritis [18,19]. Immunohistochemical (IHC) stains for C4d and BK virus were routinely performed. Renal biopsy reports and slides were reviewed by a renal pathologist (M.-C. Wen).

For clinical lupus evaluation, the original SLEDAI scores [20] were used to assess SLE status periodically. From 1984 to 1998, the basic immunosuppressive therapy after renal transplantation in our institution consisted of prednisolone, starting at 30 mg/day and tapering to 5 mg/day by the third month. Cyclosporine (CsA) was started at a dose of 10 mg kg^{-1} day^{-1} and was subsequently tapered to the lowest possible dose to maintain a blood trough of 50–150 ng/ml during a stable period. During this period, four patients had also received azathioprine at a dose of 50–100 mg/day. From 1999 to 2009, tacrolimus (TAC) at a dose of 0.2–0.3 mg kg^{-1} day^{-1} and mycophenolate mofetil (MMF) 500–750 mg twice per day were substituted for cyclosporine and azathioprine, respectively. TAC was kept at the lowest possible dose to maintain a trough level of 6–8 ng/ml during a stable period.

Statistical analysis

The Kaplan–Meier method and log-rank test were used to estimate and compare survival rates between groups. The characteristics were summarized and compared using independent two-sample *t*-tests or Wilcoxon rank sum tests as appropriate for continuous variables, and Fisher's exact test for categorical variables. A P value of less than 0.05 was considered statistically significant.

Results

Demographic, clinical and laboratory profiles

A total of 32 lupus transplant patients with a mean follow-up of 10.2±7.2 years were enrolled in this retrospective cohort study. Thirty (93.7%) patients had received native kidney biopsies, of whom 24 (80.0%) met the class IV criteria (WHO classification), three were class III, two were class V, and one was class VI. The remaining two patients who did not undergo renal biopsy were diagnosed as having SLE by meeting at least four of the revised criteria of the American College of Rheumatology. Twenty-three patients underwent graft biopsy due to graft dysfunction. The

Table 1 Pathological findings in 23 lupus patients

Pathological diagnosis	Number of items (%)
Recurrent lupus nephritis	6 (22.2)
Class I	3
Class II	1
Class IV	1
Class V + IIIA	1
Chronic rejection	9 (33.3)
Acute T cell mediated rejection	8 (22.2)
Acute anti-body mediated rejection	1 (3.7)
CNI toxicity	1 (3.7)
Acute tubular necrosis	2 (7.4)

summary of pathological diagnosis is shown in Table 1. Comparison of recurrent lupus patients (group A), the demographic data in patients with other biopsy findings (group B) and stable cases (group C) are summarized in Table 2. The mean time of disease documentation was 5.1± 4.9 years post-transplantation. There were no statistically significant differences in terms of original SLEDAI, graft function, pre-transplant dialysis period, etc.

Pathological findings of renal allograft and clinical outcomes

Of the 23 cases who received graft biopsies, chronic rejection was noted in five cases, acute cellular rejection in five cases, acute rejection with chronic rejection in three cases, acute anti-body mediated rejection with chronic rejection in one case and one case in calcineurin inhibitors nephrotoxicity (Table 1). Six (26.0%) out of 23 biopsy cases exhibited recurrent lupus nephritis (RLN), with disease onset ranging from 1.8 months

Table 2 Characteristics of 32 lupus transplant patients

Group	RLN A (*N*=6)	Non-RLN B (*N*=17)	Stable cases C (*N*=9)	*P* value
Gender				
Female	3 (50.0)	13 (76.5)	7 (77.8)	0.503
Male	3 (50.0)	4 (23.5)	2 (22.2)	
HD/PD				0.363
Hemodialysis (HD)	5 (83.3)	14 (73.1)	5 (55.6)	
Peritoneal dialysis (PD)	1 (16.7)	3 (23.1)	4 (44.4)	
Cadaveric/living donor				1.000
Cadaveric	6 (100.0)	16 (96.2)	9 (100.0)	
Living	(0.0)	1 (3.8)	0 0.0	
HBV				0.417
Negative	5 (83.3)	16 (96.2)	9 (100.0)	
Positive	1 (16.7)	1 (3.8)	0 0.0	
HCV				0.225
Negative	4 (66.7)	14 (88.5)	9 (100.0)	
Positive	2 (33.3)	3 (11.5)	0 0.0	
Transp. age	34.94±9.1	34.9±8.49	34.47±12.2	
HLA mismatch	2.50±1.5	2.80±1.48	2.31±0.9	0.945
Immunosupression				0.892
Tacro-MMF-PD	3 (50.0)	10 (58.8)	4 (44.4)	
Cyclo-Pd-(Aza)	3 (50.0)	7 (41.2)	5 (55.6)	
Age of native LN onset (years)	29.71±8.32	29.15±7.99	29.96±11.69	0.975
Time of LN onset to ESRD	2.16±2.13	2.57±3.43	2.86±2.46	0.909
Pre-transp. dialysis time (years)	3.07±3.04	3.14±2.94	1.94±1.35	0.615
Time of biopsy post-	5.14±4.96	0.72±0.92	NA	0.379
24-h urine protein (g/day)	0.86±1.18	0.72±0.92	0.02±1.76	0.040
SLEDAI scores (Bx)	3.33±3.27	2.07±2.74	0.89±1.76	0.212
Serum ANA	3	5	3	0.657
Serum anti-dsDNA	2	1	1	1.000
Low titer of serum C3/C4	4	4	2	0.168
Creatinine (mg/dl) (Bx)	1.97±0.53	2.75±1.88	1.21±0.26	0.001

HBV hepatitis B virus, *HCV* hepatitis C virus, *PD* predinsolone, *Cyclo* cyclosporine, *Tacro* tacrolimus, *MMF* mycophenolate mofetil, *ANA* anti-nuclear antibody, *anti-dsDNA* anti-double-stranded DNA antibody

to 11.6 years. Out of six cases, four (17.4%) were noted within the first decade post-transplantation. Three patients with recurrent lupus nephritis were classified in class I, one in class II, one in class IV and the remaining one in class III + V. The detailed pathological findings in patients with recurrent lupus nephritis are shown in Table 3. There was no apparent association in pathological classification between native kidney and graft. The mean follow-up duration was 9.9±6.5 years.

In the RLN group, one patient death and allograft loss because of pneumonia with sepsis and the other one allograft loss caused by RLN class IV while two cases of death and nine allograft failures occurred in the non-recurrent group.

In the RLN group, lupus nephritis contributed to allograft loss in one patient (A3), whose biopsy revealed typical findings of diffuse proliferative glomerulonephritis.

Serum antiphospholipid antibodies were examined and negative. Overall, 11 (34.4%) graft kidneys failed during the follow-up period with recurrent LN as the major cause of graft loss in only one case (9.1%). The other causes of graft failure included 7 (63.6%) due to chronic rejection, one due to renal artery infarction, and one due to acute tubular necrosis (ATN). Comparisons among groups revealed that a superior graft survival was noted in group C with stable cases which reached a statistic significance (P=0.044). However, comparisons between group A and B, there was no significant difference (P=0.257) (Fig. 1). As for patient survival, there was no difference among the groups.

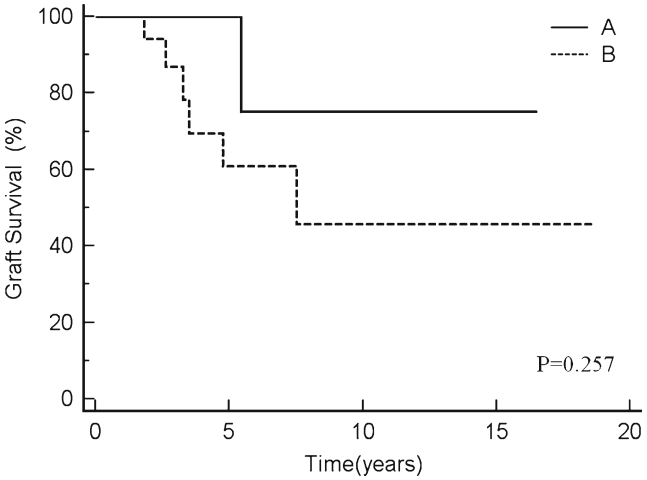

Fig. 1 Comparisons of graft survival in groups A and B using the Kaplan–Meier method and log-rank test. The results analysis demonstrated insignificantly different between both groups (P=0.257)

Treatment of recurrent lupus nephritis

Steroid pulse therapy with 500 mg methylprednisolone for 3 consecutive days was administered to patients with recurrent lupus nephritis, except one (A3) with RLN class IV who also had hepatitis B virus-related liver cirrhosis.

The dose of MMF was adjusted to a higher level when possible. In most cases, serum creatinine returned to baseline level and proteinuria subsided later. Of note, case A4 displayed heavy proteinuria (2.8 g/day), low C3 complement

Table 3 Pathological findings of biopsy-proven recurrent lupus nephritis in six lupus transplants

Patient	Renal transplant biopsy						
	Light microscopy	Immunofluorescence GBM deposit	Electron microscopy EDD	LN class Tx ISN/RPS	Banff ('97)	IF/TA	CR
A1	Glomeruli show normal cellularity	IgG(2+), IgM(1+), C′1q(2+), C′3(1+), IgA(1+), Fib(1+)	Mesangial	Class I	Negative	None	None
A2	Mesangial proliferative GN	IgG(1+), IgM(1+), C′1q(3+), C′3(3+)	Mesangial, subendothelia	Class II	Negative	Grade II	None
A3	Glomeruli are big in size, with diffuse proliferative change, loop thickening, hyaline thrombi	IgG(2+), IgM(1+) C′1q(3+), C′3, (3+), IgA(2+), Fib(1+)	Mesangial, subendothelia	Class IV	Negative	Grade I	Grade Ib
A4	Glomerular hypercellular with endocapillary proliferation; loop thickening with wire loop change,	IgG(4+), IgM(3+), C′1q(2+), C′3(3+), IgA(2+)	Mesangial, subendothelial	Class V + IIIA 20% cellular crescent	Negative	Grade I	None
A5	Glomeruli show normal cellularity	IgG(1+), IgM(2+), C′3(1+), IgA(1+)	Mesangial	Class I	AR, grade 1B	Grade I	None
A6	Glomeruli show normal cellularity	IgG (1+),IgM(1+), C′3(1+)	Mesangial	Class I	AR, grade 1A	Grade I	None

EDD electron-dense deposits, *AR* acute T-cell mediated rejection, *CR* chronic rejection, *IF/TA* interstitial fibrosis and tubular atrophy

levels, and elevated anti-ds DNA antibodies at 3 years post-transplantation, while her creatinine level was 1.3 mg/dl. Compared to native kidney findings for class IV, renal graft biopsy revealed class V + IIIA with 20% cellular crescent formation and without acute rejection or chronic allograft nephropathy. Significant histological transformation was observed in the graft kidney. Following steroid pulse therapy in this patient, urine protein had decreased to <0.5 mg/dl and stabilized. A follow-up biopsy was performed in two cases after 3 months, and no remarkable change was found in either case.

Discussion

In the current study, the overall recurrence rate of lupus nephritis was 26.1% in patients with allograft biopsy and only 4% was noted in severe proliferative recurrence lupus nephritis. Although it may have been underestimated, a protocol biopsy was not performed in the study and subtle recurrence may have been missed. Half of our recurrent cases had class I lesions, which exhibited a normal appearance under light microscopy but revealed immune complex deposits under immunofluorescence (IF) and electron-microscopic (EM) study. This highlights the necessity of immunofluorescence and electron-microscopic examinations in the diagnosis of subtle recurrence in lupus kidney transplants [21,22]. Subtle RLN has recently drawn much attention; however, the clinical significance of the recurrence remains unknown. In our study, there was no significant difference between groups A and B, implying that recurrence lupus nephritis was not necessarily a poor indicator of graft survival when compared to other entities in graft dysfunction. Furthermore, notably, a significant better graft survival was noted in group C cases who were clinically stable but may be underlying with or without recurrence LN.

Taken together, it is believed that the mild RLN was not so harmful. In fact, most of our graft loss was due to chronic rejection rather than recurrence. Only one out of 32 cases had graft loss due to RLN. The good response to treatment with steroid pulse therapy and a larger dosage of MMF is consistent with the finding that most of the recurrence cases were mild (class I to II), because all of the transplant patients were already under potent immunosuppression and an occurrence of lupus nephritis in severe form was less likely. For lupus nephritis patients without transplantation, the treatment with steroid and MMF also resulted in a good response [23].An even more satisfactory response can be anticipated if these patients are also treated with one of the calcineurin inhibitors, as were our transplant patients. However, the occurrence of higher grade recurrent lupus nephritis still should not be overlooked while lupus transplants with graft dysfunction.

Interestingly, in our RLN patients, one case (A4) with allograft histological transformation from class IV to V + III was noted after kidney transplantation and the graft function remains stable till now.

We have tried to identify possible clinical parameters that could differentiate patients with or without lupus nephritis recurrence. Unfortunately, none of them were effective for this purpose. The original SLEDAI scores while undergoing kidney allograft biopsy, an indicator of disease activity, were higher in the recurrence group but did not reach statistical significance.

In conclusion, we have demonstrated that recurrent lupus nephritis was not uncommon among a group of Chinese renal transplant recipients, however, was relatively mild in most cases. The major cause of allograft failure in these patients is chronic rejection rather than recurrence. The clinical SLEDAI score alone is insufficient to predict the recurrence of lupus GN; hence, renal biopsy is crucial for early diagnosis and useful to differentiate from other etiologies of allograft dysfunction. The recurrence was potentially treatable and not precluded for receiving transplantation.

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Disclosures None.

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