

Glomerular Podocytopathy in Patients with Systemic Lupus Erythematosus

Steven W. Kraft,* Melvin M. Schwartz,[†] Stephen M. Korbet,* and Edmund J. Lewis*

*Section of Nephrology, Department of Medicine, and [†]Department of Pathology, Rush University Medical Center, Chicago, Illinois

A series of patients with systemic lupus erythematosus (SLE) and proteinuria were studied to determine whether nephrotic-range proteinuria was associated with diffuse epithelial cell foot process effacement in the absence of peripheral glomerular immune aggregate deposition. Biopsies from patients with known or suspected SLE and a histologic diagnosis of (1) normal by light microscopy, (2) mesangial proliferative glomerulonephritis, or (3) focal segmental glomerulosclerosis were studied. Biopsies were excluded when they demonstrated endocapillary proliferation or necrosis by light microscopy or electron-dense glomerular basement membrane deposits by electron microscopy. Patients were required to fulfill four of 11 American Rheumatologic Association criteria for the diagnosis of SLE, and proteinuria could not be associated with nonsteroidal anti-inflammatory drug use. Eighteen biopsies were studied, eight from patients with nephrotic-range proteinuria (≥ 3 g/d) and 10 from patients with nonnephrotic proteinuria. The time from diagnosis of SLE to biopsy was shorter for nephrotic patients than for nonnephrotic patients. Seven of eight biopsies from nephrotic patients demonstrated at least 80% foot process effacement, whereas no biopsy from a nonnephrotic patient exhibited $>20\%$ effacement. There were no other significant pathologic differences between the nephrotic and nonnephrotic patients. The single common morphologic feature associated with nephrotic proteinuria was diffuse visceral epithelial cell foot process effacement. It is concluded that the development of nephrotic-range proteinuria in patients with SLE without peripheral immune aggregate deposition or endocapillary proliferation on renal biopsy is more likely a manifestation of SLE than the coexistence of idiopathic minimal-change glomerulopathy and SLE.

J Am Soc Nephrol 16: 175–179, 2005. doi: 10.1681/ASN.2004050350

The nephrotic syndrome in patients with systemic lupus erythematosus (SLE) is usually associated with immune aggregate deposition in the glomerular capillary wall, frequently accompanied by endocapillary proliferation or necrosis (1,2). There are reports of patients who have SLE who developed the nephrotic syndrome in the absence of either significant capillary wall immune complex deposition or cellular proliferation; in most of these cases, the renal biopsies demonstrated widespread effacement of the epithelial cell foot processes similar to that seen in minimal-change glomerulopathy (3–10). The implication of these observations is that there may be a common pathogenetic mechanism, independent of the deposition of immune aggregates, that accounts for the proteinuria in these patients. Given the statistical improbability of concurrent active SLE and idiopathic minimal-change glomerulopathy in an individual patient (4), we studied our own series of patients who had SLE with proteinuria to determine whether nephrotic-range proteinuria was associated with dif-

fuse epithelial cell foot process effacement in the absence of peripheral glomerular immune aggregate deposition.

Materials and Methods

We conducted a retrospective, clinicopathologic analysis of 470 renal biopsies from patients with SLE that were submitted for evaluation at Rush University Medical Center from 1976 to 2003. The biopsies were processed by standard techniques for histology, immunofluorescence microscopy, and electron microscopy. Biopsies from patients with known or suspected SLE and a preliminary histologic diagnosis of (1) normal by light microscopy, (2) mesangial proliferative glomerulonephritis, or (3) focal segmental glomerulosclerosis (FSGS) were reevaluated by a renal pathologist who had no knowledge of the level of protein excretion, response to treatment, or clinical outcome. Biopsies were excluded from the study when they demonstrated endocapillary proliferation or necrosis by light microscopy or electron-dense glomerular basement membrane deposits by electron microscopy or when electron micrographs were not available. Clinical, laboratory, and serologic data were obtained from chart review. Patients who did not fulfill four of 11 American Rheumatologic Association criteria for the diagnosis of SLE (11,12) were excluded. The use of a nonsteroidal anti-inflammatory drug (NSAID) was evaluated.

Fifty-six biopsies met the preliminary histologic inclusion criteria and were evaluated further. Thirty-six biopsies were excluded as a result of the presence of basement membrane granular deposits (fluorescence microscopy), significant subepithelial or intramembranous electron-dense deposits, or evidence of active or resolving segmental endocapillary proliferation. Of the remaining 20 biopsies, two patients did not

Received May 4, 2004. Accepted October 14, 2004.

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Stephen M. Korbet, Section of Nephrology, Department of Medicine, Rush University Medical Center, 1426 W. Washington Boulevard, Chicago, IL 60607. Phone: 312-850-8434; Fax: 312-829-3887; E-mail: skorbet@aol.com

fulfill four of 11 American Rheumatologic Association criteria and were excluded.

Pathology Studies

Pathologic material on the 18 study patients included histologic sections stained for hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome, and methenamine silver periodic acid-Schiff (Jones) stains; detailed surgical reports; and photographs of the fluorescence and electron microscopy. Total glomeruli and the number of glomeruli showing segmental and global sclerosis were recorded for each biopsy. Mesangial proliferation was semiquantified (0, none; 1+, <3 cells/mesangial area; 2+, 4 to 5 cells/mesangial area; and 3+, >6 cells/mesangial area) and was considered present when it was >1+. The diagnosis of acute tubular necrosis (ATN) injury was established by the presence of tubules showing thinning of the epithelium, loss of brush border with or without regenerative changes, and absent tubular basement membrane thickening. The presence and location of glomerular immune deposits (mesangial or granular basement membrane) and electron-dense deposits (subepithelial, intramembranous, subendothelial, and mesangial) were recorded. The extent of epithelial cell foot process effacement (0 to 100%) was estimated after examination of all of the electron photomicrographs of nonsclerotic glomeruli in each study and control case. There were 10.75 ± 1.91 (mean \pm SD) photographs per case, including scanning- ($\times 6250$ to 7500), intermediate- ($\times 10,000$ to $18,750$), and high- ($\times 30,000$) magnification photographs of the capillary walls and mesangium. The photographs contained 26.25 ± 7.73 complete and partial glomerular capillaries/biopsy.

Clinical Studies and Laboratory Examination

Demographic, clinical, and laboratory information at the time of renal biopsy and at follow-up was obtained on each patient. Clinical records were reviewed to determine the patients' gender, age, BP, level of protein excretion, serum creatinine, serum albumin, and lupus serology (antinuclear antibody [ANA] titer, anti-DNA titer, and C3) at the time of biopsy. The cases were dichotomized on the basis of the level of proteinuria at the time of biopsy, into nephrotic (≥ 3 g/d) or nonnephrotic (<3.0 g/d) proteinuria. The duration of SLE was defined as the time from presentation with SLE to the time of presentation with

nephrotic or non-nephrotic proteinuria. Microscopic hematuria was defined as >5 red blood cells/high-powered field.

Statistical Analyses

Continuous variables were compared using the unpaired *t* test, and categorical variables were compared using the Fisher exact test. *P* < 0.05 was considered significant.

Results

The clinical characteristics at biopsy of the nephrotic and nonnephrotic patients are shown in Table 1. Nephrotic proteinuria was observed in eight patients, and 10 patients were nonnephrotic. The age (range: nephrotic, 8 to 59 yr; nonnephrotic, 10 to 60 yr) and gender (female: nephrotic, 88% and nonnephrotic, 100%) were similar among both groups at biopsy. There was no significant difference in BP or the presence of microscopic hematuria. The serum creatinine at biopsy was significantly higher in the nephrotic group, and this was attributed to the presence of acute renal failure in four of the nephrotic patients (three requiring dialysis) at the time of biopsy. In no case was the onset of proteinuria related to the use of NSAID, and there was no history of NSAID use in the patients with acute renal failure. Although there were no significant differences in ANA titer, C3 level, or the proportion of patients with an elevation in anti-dsDNA titer (Table 1), nephrotic patients had higher ANA titers and lower C3 levels and a larger proportion of patients with an ANA titer $>1:1280$, C3 <80 mg/dl, and an elevated anti-dsDNA titer than nonnephrotic patients. Furthermore, nephrotic proteinuria was observed soon after the diagnosis of SLE. The time from diagnosis of SLE to presentation with proteinuria was significantly shorter in nephrotic patients compared with nonnephrotic patients (1.4 ± 2.3 versus 29.9 ± 51.3 mo; *P* < 0.05). All eight nephrotic patients presented within 6 mo of the onset SLE (in ≤ 1 mo in six

Table 1. Clinical characteristics at biopsy^a

	Nephrotic	Nonnephrotic	P Value
<i>n</i>	8	10	
Male/female	1/7	0/10	0.44
Age (yr)	32 ± 16	28 ± 16	0.63
Systolic BP (mmHg)	124 ± 18	120 ± 21	0.71
Diastolic BP (mmHg)	78 ± 20	76 ± 17	0.78
Proteinuria (g/d)	7.2 ± 3.5	0.82 ± 0.70	<0.001
Creatinine (mg/dl)	3.8 ± 3.1	0.9 ± 0.4	<0.01
Albumin (g/dl)	2.1 ± 0.5	3.8 ± 0.5	<0.001
Cholesterol (mg/dl)	232 ± 79	155 ± 36	<0.05
Hematuria (<i>n</i>)	5	6	1
ANA titer (dilution)	$1:2740 \pm 3368$	$1:1608 \pm 3071$	0.47
ANA $\geq 1:1280$ (<i>n</i>)	7	4	0.06
C3 (mg/dl)	62 ± 16	80 ± 48	0.34
C3 ≤ 80 mg/dl (<i>n</i>)	7	6	0.31
Elevated anti-dsDNA (<i>n</i>)	6	3	0.15
SLE duration (mo)	1.4 ± 2.3	29.9 ± 51.3	<0.05

^aResults of continuous variables are mean \pm SD. ANA, antinuclear antibody; SLE, systemic lupus erythematosus.

patients) compared with only five nonnephrotic patients ($P < 0.05$). The remaining five nonnephrotic patients presented with proteinuria >1 yr after the diagnosis of SLE.

Pathologic findings are summarized in Table 2. Three biopsies were essentially normal by light microscopy, seven demonstrated mesangial proliferation alone, and eight had segmental areas of epithelial cell proliferation or sclerosis either alone ($n = 1$) or accompanied by mesangial proliferation ($n = 7$). The histology of the groups was similar. Two biopsies with segmental sclerosis, both in the nephrotic group, had the glomerular morphology of the cellular/collapsing variant of FSGS; both of these patients tested negative for HIV at least twice and had a negative evaluation of renal tissue for parvovirus B19 (Cell Marque, clone R92F6), and neither was on pamidronate. ATN was noted in three nephrotic cases. By immunofluorescence microscopy, mesangial deposits of IgG were noted in a similar proportion of nephrotic and nonnephrotic biopsies. Peripheral capillary deposits of immunoglobulins or complement components were not seen in either group. By electron microscopy, electron-dense deposits were noted in the mesangium in a similar proportion of nephrotic and nonnephrotic biopsies. No subendothelial or subepithelial electron-dense deposits were observed in any biopsies.

The degree of foot process effacement was significantly different in the nephrotic and nonnephrotic patients. Diffuse effacement ($\geq 80\%$) of the epithelial cell foot processes was seen in seven (88%) of eight biopsies in the nephrotic group, with six having 100% effacement. In contrast, no biopsy in the nonnephrotic group had $>20\%$ effacement. Thus, the degree of foot process effacement was the only morphologic feature that was significantly different between the two groups.

Follow-up was obtained in all nephrotic patients and ranged from 3 to 48 mo. All eight nephrotic patients were treated with prednisone, and four also received cytotoxic agents. Six of the eight treated patients experienced a significant reduction of proteinuria to subnephrotic levels, although only one patient

had undetectable proteinuria at last follow-up. A recovery of renal function was observed in all three patients who presented with ATN. Of the two patients who did not respond to therapy, one presented with advanced renal failure associated with the cellular/collapsing variant of FSGS; she remained dialysis dependent until dying of sepsis 7 mo after her biopsy. The other patient developed renal insufficiency and ultimately dialysis dependence despite therapy with steroids, azathioprine, mycophenolate mofetil, and cyclophosphamide.

Discussion

Our study describes a subset of patients who had SLE, developed nephrotic-range proteinuria without evidence of either glomerular peripheral capillary immune complex deposits or endocapillary proliferation, and had complete or near-complete podocyte foot process effacement. In contrast, biopsies from patients who had lupus nephritis without peripheral capillary loop deposits and had nonnephrotic proteinuria were shown to have less or no podocyte foot process effacement. In both the nephrotic and nonnephrotic groups, light microscopy ranged from normal to mesangial proliferation to segmental glomerulosclerosis, making abnormal visceral epithelial cell morphology the only histologic factor distinguishing the patients with nephrotic-range proteinuria.

Our observations support the published findings of Hertig *et al.* (4), who reported a series of 11 patients who had SLE and developed the nephrotic syndrome and were found to have either minimal-change glomerulopathy or FSGS on renal biopsy. On the basis of disease prevalence data from their region, they estimated the probability of idiopathic minimal-change disease or idiopathic FSGS occurring in a patient with SLE to be <1 in 10,000. The observed prevalence of concurrent idiopathic minimal-change glomerulopathy or FSGS in the patient population reported by Hertig *et al.* was far higher than might be expected by chance occurrence, being diagnosed in two per 132 patients with lupus nephritis evaluated at one center. Our eight

Table 2. Histologic characteristics^a

	Nephrotic	Nonnephrotic	P Value
<i>n</i>	8	10	
Total glomeruli	29 \pm 13	27 \pm 13	0.75
Normal light microscopy (<i>n</i>)	1	2	1
Mesangial proliferation (<i>n</i>)	7	7	0.59
Segmental sclerosis (<i>n</i>)	4	4	1
Segmental scars	6 \pm 11	1 \pm 1	0.15
Acute tubular necrosis (<i>n</i>)	3	0	0.07
Mesangial deposits (<i>n</i>)			
Immunofluorescence ^b	6	8	1
Electron microscopy	5	7	1
Foot process effacement (<i>n</i>)			
$\geq 80\%$	7	0	<0.001
$\leq 20\%$	1	10	<0.001

^aResults of continuous variables are mean \pm SD.

^bIgG deposition.

cases of nephrotic syndrome were derived from a pool of 470 renal biopsies performed on patients with lupus nephritis. As in our series, Hertig *et al.* observed that patients presented with the nephrotic syndrome early in the course, soon after the onset of symptoms and diagnosis of SLE in the majority of cases.

Dube *et al.* (3) reported a series of seven SLE patients who presented with the nephrotic syndrome and were found to have diffuse podocyte effacement on renal biopsy. All seven patients had a diagnosis of minimal-change glomerulopathy, but five were received a diagnosis of class II lupus nephritis on the basis of the presence of mesangial immune complex deposition. One biopsy in this series was completely negative for mesangial deposits by electron microscopy. This finding is consistent with our series and with other published cases of minimal-change glomerulopathy in SLE, in which mesangial deposits were commonly present (5,8,9). These observations suggest that published literature suggesting that the mesangial glomerulopathy of lupus (World Health Organization class II) could occur in patients with the nephrotic syndrome may actually be better explained by the presence of a primary pathologic process involving the glomerular epithelial cell.

Although the cause of idiopathic minimal change glomerulopathy is unknown, the Shalhoub hypothesis holds that a product of aberrant T cell function is responsible for glomerular epithelial cell injury resulting in diffuse podocyte effacement (13). There is growing evidence that activated T cells may indeed express factors that are responsible for abnormal urine protein excretion (14,15). Evidence that supports abnormal T cell cytokine expression has been described in minimal-change glomerulopathy (16,17). Sahali *et al.* (18) identified overexpression of several DNA transcripts from patients with minimal-change glomerulopathy that suggest T cell activation. Similarly, glomerular epithelial cell injury resulting from a “circulating factor” of presumed T cell origin has been implicated in the lesions of focal segmental sclerosis (19,20,21). These findings raise the question of whether activated T cells could similarly be implicated in the pathogenesis of the podocyte lesion and proteinuria that we describe. T cell activation seems to play an important role in the pathogenesis of SLE by altering the production of cytokines and the expression of cellular adhesion molecules, as well as inducing B cells to produce autoantibodies (22). Therefore, one might speculate that the underlying mechanism of SLE-related podocytopathy, as proposed in idiopathic minimal-change glomerulopathy, could similarly be mediated by activated T cells. The concurrent presentation of clinical renal abnormalities (nephrotic syndrome) and evidence of active SLE in our patients supports this hypothesis.

Previous reports of patients with SLE and podocytopathy have shown the nephrotic syndrome to be responsive to steroid therapy. Dube *et al.* (3) found that all patients who followed up within 6 wk of initiating therapy had a significant reduction in proteinuria, although none had achieved a complete remission. Hertig *et al.* (4) observed a remission in the majority of patients at last follow-up. A favorable response to therapy seen in the majority of patients in our series is in agreement with the results of those reports.

We have confirmed that nephrotic-range proteinuria does

occur in patients with SLE in the absence of glomerular capillary wall immune complex deposition and endocapillary proliferation and have identified diffuse effacement of the visceral epithelial cell foot processes as the single morphologic feature associated with this clinical phenomenon. The frequency of these cases and the observation that the onset of the nephrotic syndrome frequently correlates with the onset of clinical systemic features of SLE seem to call for the interpretation that the podocytopathy is the result of active lupus more likely than the coexistence of two separate but concurrent diseases, SLE and minimal-change glomerulopathy. These findings suggest that renal biopsies should be evaluated for the presence of “lupus podocytopathy,” as it can be responsible for the nephrotic syndrome in patients with SLE independent of peripheral glomerular capillary immune aggregate deposition or cellular proliferation and warrants institution of appropriate therapy.

Acknowledgments

We thank Dr. Farahnak Assadi (Rush University Medical Center, Department of Pediatrics) and Drs. Earl Smith and Mohammed Ahmed (Mount Sinai Hospital, Chicago, IL) for the contribution of clinical data in six cases in this series.

References

- Pollak VE, Pirani CL, Schwartz FD: The natural history of the renal manifestations of systemic lupus erythematosus. *J Lab Clin Med* 63: 537–550, 1964
- Baldwin DS, Gluck MC, Lowenstein J, Gallo GR: Lupus nephritis: Clinical course as related to morphologic forms and their transitions. *Am J Med* 62: 12–30, 1977
- Dube GK, Markowitz GS, Radhakrishnan J, Appel GB, D’Agati VD: Minimal change disease in systemic lupus erythematosus. *Clin Nephrol* 57: 120–126, 2002
- Hertig A, Droz D, Lesavre P, Grünfeld J, Rieu P: SLE and idiopathic nephrotic syndrome: Coincidence or not? *Am J Kidney Dis* 40: 1179–1184, 2002
- Stankeviciute N, Jao W, Bakir A, Lash JP: Mesangial lupus nephritis with associated nephrotic syndrome. *J Am Soc Nephrol* 8: 1199–1204, 1997
- Nishihara G, Nakamoto M, Yasunaga C, Takeda K, Matsuo K, Urabe M, Goya T, Sakemi T: Systemic lupus erythematosus in a patient with remitting minimal change nephrotic syndrome. *Clin Nephrol* 48: 327–330, 1997
- Perakis C, Arvanitis A, Sotsiou F, Emmanouel DS: Nephrotic syndrome caused by minimal-change disease in a patient with focal proliferative SLE nephritis (WHO III) in remission. *Nephrol Dial Transplant* 13: 467–470, 1998
- Hunley TE, Yared A, Fogo A, MacDonell RC: Nephrotic syndrome in an adolescent: The cry of the wolf. *Am J Kidney Dis* 31: 155–160, 1998
- Makino H, Haramoto T, Shikata K, Ogura T, Ota Z: Minimal-change nephrotic syndrome associated with systemic lupus erythematosus. *Am J Nephrol* 15: 439–441, 1995
- Hickman PL, Nolph KD, Jacobs R, Luger AM, Walker SE: Idiopathic focal segmental glomerulosclerosis in a patient with systemic lupus erythematosus: An unusual combination. *Am J Kidney Dis* 23: 582–586, 1994
- Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ: The 1982

- revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25: 1271–1277, 1982
12. Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 40: 1725, 1997
 13. Shalhoub RJ: Pathogenesis of lipoid nephrosis: A disorder of T-cell function. *Lancet* 2: 556–560, 1975
 14. Cunard R, Kelly CJ: T cells and minimal change disease. *J Am Soc Nephrol* 13: 1409–1411, 2002
 15. Koyama A, Fujisaki M, Kobayashi M, Igarashi M, Narita M: A glomerular permeability factor produced by human T cell hybridomas. *Kidney Int* 40: 453–460, 1991
 16. Yap HK, Cheung W, Murugasu B, Sim SK, Seah CC, Jordan SC: Th1 and Th2 cytokine mRNA profiles in childhood nephrotic syndrome: Evidence for increased IL-13 mRNA expression in relapse. *J Am Soc Nephrol* 10: 529–537, 1999
 17. Van Den Berg JG, Aten J, Annink C, Ravesloot JH, Weber E, Weening JJ: Interleukin-4 and -13 promote basolateral secretion of H(+) and cathepsin L by glomerular epithelial cells. *Am J Physiol Renal Physiol* 282: F26–F33, 2002
 18. Sahali D, Pawlak A, Valanciute A, Grimbirt P, Lang P, Remy P, Bensman A, Guellaen G: A novel approach to investigation of the pathogenesis of active minimal-change nephrotic syndrome using subtracted cDNA library screening. *J Am Soc Nephrol* 13: 1238–1247, 2002
 19. Korbet SM, Schwartz MM, Lewis EJ: Recurrent nephrotic syndrome in renal allografts. *Am J Kidney Dis* 11: 270–276, 1988
 20. Trachtman H, Greenbaum LA, McCarthy ET, Sharma M, Gauthier BG, Frank R, Warady B, Savin VJ: Glomerular permeability activity: Prevalence and prognostic value in pediatric patients with idiopathic nephrotic syndrome. *Am J Kidney Dis* 44: 604–610, 2004
 21. McCarthy ET, Sharma M, Sharma R, Falk RJ, Jennette JC: Sera from patients with collapsing focal segmental glomerulosclerosis increase albumin permeability of isolated glomeruli. *J Lab Clin Med* 143: 225–229, 2004
 22. Wüthrich RP, Jevnikar AM, Kelley VR: Understanding lupus nephritis: Unraveling the pathogenesis through molecular approaches in murine models. In: *Lupus Nephritis*, edited by Lewis EJ, Schwartz MM, Korbet SM, New York, Oxford University Press, 1999, pp 103–125