Mesangial Lupus Nephritis with Associated Nephrotic Syndrome

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Abstract. Patients with mesangial proliferative lupus glomerulonephritis (World Health Organization class II) generally have minimal evidence of clinical renal disease with mild proteinuria or hematuria and normal renal function. However, there have been several reports of patients with mesangial lupus with nephrotic-range proteinuria. In this report, we present two additional cases and review the literature. Of seven reported cases, persistent nephrotic syndrome was observed in four, morphologic transformation occurred in three, and all but one presented with varying degrees of azotemia. These cases reinforce the concept that in systemic lupus erythematosus, laboratory findings may not correlate well with the underlying glomerular lesion, and therefore, the renal biopsy is an essential clinical tool in the approach to lupus nephritis. (J Am Soc Nephrol 8: 1199–1204, 1997)

It has been widely accepted that patients with mesangial lupus glomerulonephritis (World Health Organization [WHO] class II) generally have minimal evidence of clinical renal disease with mild proteinuria or hematuria and normal renal function (1,2). The development of nephrotic syndrome in a patient with mesangial nephritis may signify transformation to another form of lupus nephritis. However, there have been several reports of patients with mesangial nephritis with nephrotic-range proteinuria in the absence of transformation (3–7). This study presents the unusual cases of two patients who exhibited severe renal disease, although the kidney biopsy showed only mesangial lupus nephritis.

Case Report 1
An African-American woman 36 yr of age with no significant past medical history was seen because of a several-day history of arthralgias and swelling of the face, hands, and legs. She had no urinary complaints, myalgias, fever, rash, or sore throat. Examination revealed mild pretibial edema and a patch of skin thickening on the left flank consistent with morphea. Her laboratory results were as follows: serum albumin level, 1.0 g/dl; cholesterol, 368 mg/dl; creatinine, 1.6 mg/dl; and sedimentation rate, 104 mm/h. ANA was positive, single-stranded DNA 101 U/ml (normal, up to 99 U/ml), and ribonuclear protein (RNP) 331 U/ml (normal, up to 83 U/ml). Urinalysis showed 4+ proteinuria. A diagnosis of systemic lupus erythematosus (SLE) was made, which was supported by the presence of five criteria for the classification of SLE (including skin involvement, renal disease, leukopenia less than 4000/mm³, a positive antinuclear antibody [ANA], and a positive anti-Smith [Sm] that was detected at a later point) (8). Ibuprofen, 600 mg three times a day, was prescribed for the relief of joint pain. One week later, she was referred to our renal clinic because her creatinine increased to 3.0 mg/dl. Ibuprofen was discontinued, and furosemide was prescribed for the edema. However, the next week the patient returned complaining of nausea, vomiting, general weakness, and worsening of leg edema. She denied illicit drug use. Her family history was significant in that an older sister had SLE and scleroderma.

Her blood pressure was 140/92 mmHg and her weight was 226 lb. Marked leg edema and ascites were present. Other results were as follows: blood urea nitrogen (BUN), 61 mg/dl; serum creatinine, 5.0 mg/dl; total protein, 3.7 g/dl; albumin, 0.7 g/dl; and cholesterol, 537 mg/dl. The hemoglobin was 12.6 g/dl, hematocrit 37.8%, white blood cell count 3.8 × 10³/μl with a normal differential, and the platelet count was 256,000/mm³. A urinalysis showed a specific gravity of 1.030, a pH of 7.5, and more than 300 mg/dl protein. Microscopic examination revealed three white blood cells, five red blood cells, and one renal epithelial cell cast per high-power field, as well as fat droplets. A 24-h urine collection contained 20 g of protein. A second ANA titer was positive in a speckled pattern, and RNP and Sm antibodies were also positive. Serum C3 and C4 were normal, but total serum hemolytic complement was 87 U/ml (normal, 130 to 410 U/ml). Tests for hepatitis C antibody, hepatitis B surface antigen, human immunodeficiency virus antibody, and rapid plasma reagin were all negative. Renal ultrasound demonstrated two normal-sized kidneys, and a magnetic resonance angiogram was negative for renal vein thrombosis.
Figure 1. Light microscopy (A) reveals minimal mesangial hypercellularity. (Hematoxylin & eosin stain; magnification, ×460). In addition, dilated tubules with flattened epithelial cells (B) signify the presence of acute tubular necrosis. (Hematoxylin & eosin stain; magnification, ×310). Immunofluorescence microscopy (C) reveals minimal granular IgG deposits in the mesangium. (Magnification, ×460). Four months later, a second biopsy (D) reveals minimal mesangial accentuation (silver-methenamine stain, magnification, ×320).
A kidney biopsy specimen contained 14 glomeruli that demonstrated minimally increased mesangial cellularity (Figure 1A). However, the most dramatic changes were seen in the tubules, which were dilated and lined by flattened epithelial cells, a picture consistent with acute tubular necrosis (ATN) (Figure 1B). On electron microscopy, the glomerular capillary basement membrane was of normal thickness, and one-half of the podocytes exhibited effacement of the foot processes. Microtubular structures were seen in endothelial cells. The mildly expanded mesangium contained rare electron-dense deposits. Immunofluorescence microscopy revealed minimal deposition of IgG, IgA, IgM, and C3 in the mesangium and along some segments of the capillary walls (Figure 1C). Overall, the findings were consistent with the diagnosis of mild mesangial proliferative lupus glomerulonephritis and ATN.

The patient was treated initially with intravenous methylprednisolone 1 g daily for 3 d and then given 60 mg of prednisone daily. Over the next several weeks, the serum creatinine decreased to 0.9 mg/dl, but the patient remained severely nephrotic. Over the course of 2 mo, she was hospitalized twice because of massive edema and weight gain of up to 70 lb. Despite high doses of corticosteroids and diuretics. We therefore started monthly intravenous infusions of cyclophosphamide and tapered the prednisone dose to 40 mg/d. After four monthly doses of cyclophosphamide, however, edema gradually increased and she had two additional lengthy hospital admissions for intravenous diuretic therapy. At the time of the second hospitalization, BUN was 44 mg/dl, serum creatinine 3.4 mg/dl, and total serum hemolytic complement 94 U/ml. The 24-h urine protein excretion remained at 20 g.

To rule out the possibility of morphologic transformation, a second kidney biopsy was done 5 mo after the first biopsy. The specimen contained 33 glomeruli, one of which showed global sclerosis. The glomeruli showed minimal mesangial accentuation with patent capillaries (Figure 1D). The tubulointerstitial component was normal. By electron microscopy, segmental expansion of mesangial matrix was seen. No electron-dense deposits were seen along the basement membrane or in the mesangium. Approximately 80% of the epithelial foot processes were effaced. Immunofluorescence microscopy showed small amounts of IgG and C3 along the capillary walls.

Treatment was initiated with cyclosporin A, 3.0 mg/kg per day. After 1 mo of treatment, her edema decreased dramatically and she maintained a weight of 158 lb on high doses of furosemide and metolazone. In addition, the serum creatinine decreased to 1.0 mg/dl and urinary protein excretion to 10 g/d.

Case Report 2

An African-American woman 33 yr of age presented with a 2-wk history of pleuritic chest pain and shortness of breath. She was treated with ibuprofen without improvement. One week later, she returned with complaints of sharp left-sided chest pain. A chest x-ray showed bilateral pleural effusions, and erythromycin was prescribed for a suspected pneumonia. Two weeks later, the patient was admitted to the hospital, still complaining of chest pain and diffuse arthralgias. Laboratory data included a positive ANA, Sm antibody 130,000 U/ml (normal, up to 90 U/ml), RNP 1,860,000 U/ml (normal, up to 83 U/ml), Sjögren’s syndrome A 206 U/ml (normal, up to 96 U/ml), C3 94 mg/dl (normal, 83 to 177 mg/dl), C4 14.6 mg/dl (normal, 15 to 45 mg/dl), BUN 15 mg/dl, and serum creatinine 0.7 mg/dl. Urinalysis showed no protein, specific gravity of 1.024, and a pH of 5.0. Microscopic examination revealed three red blood cells and two to five white blood cells per high-power field. The patient was treated with high-dose prednisone, Plaquenil, and indomethacin. Three months later she was noted to have proteinuria. A 24-h urine collection showed 4.3 g of protein. Indomethacin was discontinued, but 8 wk later she was referred to our renal clinic because she continued to have nephrotic-range proteinuria. At that time, prednisone had been tapered to 12.5 mg/d. The patient had no rash or fever and denied using illicit drugs. Her family history was unremarkable.

The blood pressure was 120/80 mmHg and the weight 147 lb. Except for a trace of pedal edema, the physical examination was normal. The BUN was 13 mg/dl, serum creatinine 0.9 mg/dl, cholesterol 311 mg/dl, albumin 2.7 g/dl, and total protein 6.5 g/dl. The hemoglobin was 13.2 g/dl, white blood cell count 14.8 × 10^3/mm^3, and platelet count 137,000. Urinalysis showed a specific gravity of 1.022, a pH of 5.0, and protein more than 300 mg/dl. Microscopic examination revealed one white blood cell and three hyaline casts per high-power field. A second 24-h urine collection showed 4.2 g of protein. Hepatitis B surface antigen and hepatitis C virus antibody were negative. The serum C3 and C4 levels remained normal.

A kidney biopsy contained 24 glomeruli that showed minimal mesangial accentuation (Figure 2). When examined by electron microscopy, the glomerular capillary basement membranes were of normal thickness. A few small mesangial electron-dense deposits were noted, and 60% of the podocytes showed fusion of the foot processes. Numerous clusters of endothelial microtubular structures were seen. Immunofluorescence microscopy showed minimal deposition of IgG, IgM, and C3 in the mesangium and segmentally along the capillary walls in a granular pattern (Figure 6). A diagnosis of mild mesangial lupus glomerulonephritis was made.

The patient was continued on the same doses of prednisone and Plaquesnil. She remained normotensive, had no edema, and had a stable serum creatinine of 0.9 mg/dl. Seven months later her urinary protein excretion had decreased to 1.0 g/d.

Discussion

In patients with lupus nephritis, the nephrotic syndrome is generally associated with diffuse (WHO class IV) or membranous glomerulonephritis (WHO class V). We have reported two patients with SLE and nephrotic-range proteinuria in whom the renal biopsy unexpectedly revealed a mesangial lesion. On presentation, our first patient had profound hypoaalbuminemia with consequent intravascular volume depletion, which undoubtedly predisposed her to develop ATN with the use of ibuprofen. After recovering from the ATN, the subsequent decline in renal function and the persistent nephrosis suggested a morphologic transformation. However, the second biopsy again showed a mesangial lesion. In contrast to
the refractory nephrotic syndrome seen in this patient, our second patient was relatively asymptomatic, and proteinuria diminished significantly with no alterations in therapy.

The association of mesangial lupus nephritis with clinically severe renal disease must be quite rare because there are only 13 cases reported in the English literature. Of these, the five adult and three pediatric cases reported by Cameron et al. lacked information about the clinical course (9,10). The remaining five cases (3–7), as well as our two, are summarized in Table 1. The earliest cases were reported by Baldwin et al. (3) and Zimmerman (4). In both cases, the patients later developed diffuse proliferative glomerulonephritis. The patient reported by Bakir et al. exhibited severe nephrotic syndrome as well as persistent hematuria and hypocomplementemia, was resistant to prednisone, but responded to intravenous cyclophosphamide (personal communication, A. Bakir), and transformed a year later to a membranous lesion (5). Similar to our second case, Trachtman described a woman with spontaneous remission of the nephrotic syndrome (6). In an unusual case reported by Braun et al., a young woman developed leukopenia, fever, psychosis, and renal failure. Her renal biopsy showed mesangial nephritis without ATN (7). She was treated with hemodialysis, plasmapheresis, corticosteroids, and cyclophosphamide. Dialysis was discontinued after 7 wk, and her renal function eventually recovered completely. As summarized in Table 1, persistent nephrotic syndrome was observed in four of the seven cases, morphologic transformation occurred in three, and all but one presented with varying degrees of azotemia.

The pathogenesis of the nephrotic syndrome with mesangial lupus nephritis is not clear because immune complexes are not detected in the glomerular basement membrane by immunofluorescence or electronmicroscopy. It may be that immune complex deposition in the mesangium leads to the release of cytokines, which alter glomerular permeability. A history of nonsteroidal anti-inflammatory drug (NSAID) use was present in three of the patients (Table 1). Because NSAID have been reported to cause a minimal change disease lesion with nephrotic syndrome (12), it is important to consider whether NSAID use may have played a role in these cases. As discussed earlier, the nephrotic syndrome was present before the institution of ibuprofen in our first case. However, the nephrotic syndrome developed after the initiation of NSAID use in our second case and in the case reported by Bakir et al. (5). Because of this, one cannot exclude NSAID use as a potential factor contributing to the development of proteinuria in these cases. Furthermore, our first case emphasizes the importance of avoiding NSAID in nephrotic patients with SLE.

Another consideration is that these patients might have had the coincidental occurrence of minimal change disease. How-
ever, several factors suggest that it is more likely that these patients had mesangial lupus nephritis. Although extensive deposits were not detected by electron microscopy, immunofluorescence was positive for IgG, IgM, and C3. The positive immunofluorescence is suggestive of lupus nephritis because it is more commonly negative in cases of minimal change disease (13). The presence of microtubular structures also is more supportive of lupus nephritis. In each case, only approximately 50 to 60% of the podocytes were fused. Minimal change disease is usually associated with more extensive effacement. Finally, the steroid and cyclophosphamide resistance seen in the first case is less characteristic of minimal change disease. For these reasons, although coincidental minimal change disease cannot be completely excluded, it seems more likely that these patients had mesangial lupus nephritis.

In conclusion, the two presented cases and the review of the literature illustrate that mesangial nephritis, although not usually a cause of tangible renal disease, can be associated with nephrotic-range proteinuria. These cases reinforce the concept that in SLE, laboratory findings may not correlate well with the underlying glomerular lesion, and therefore the renal biopsy is an essential clinical tool in the approach to lupus nephritis. Furthermore, the optimal therapeutic approach to the patient with mesangial lupus and the nephrotic syndrome is not well established because of the sparse number of reported cases and the variability of the clinical course. It seems reasonable, however, to reserve aggressive immunosuppression for patients with more severe manifestations of the nephrotic syndrome. A favorable early response to cyclosporine was observed in our first case report, but the long-term response remains to be seen.

References

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**Nephrology Fellowship at the University of Illinois at Chicago**

The University of Illinois College of Medicine is the largest medical school in the country. The Section of Nephrology oversees the care of a diverse population of patients and has a major commitment to patient care, teaching, and research.

The Nephrology Training Program is based at the University of Illinois at Chicago Hospital and two neighboring institutions: West Side Veterans Affairs Medical Center and Cook County Hospital. The University of Illinois at Chicago Hospital is a tertiary referral center with a full spectrum of services, including an active organ transplant program. The West Side Veterans Affairs Medical Center has a wide catchment area drawing from the west and south sides of the city. Cook County Hospital provides care for the medically indigent and has an active lupus service. Together, the three institutions provide trainees with an exposure to the full spectrum of clinical nephrology, including consultation service and an outpatient continuity clinic. In addition, fellows participate in longitudinal outpatient hemodialysis rounds and a peritoneal dialysis clinic. The Renal Transplant Program at the University performs more than 70 renal transplants per year, and trainees are involved in the immediate postoperative and long-term management of these recipients. Three nephrology fellows are accepted into the training program each year. The first and second year are primarily clinical, with an option of a third for laboratory research. An active didactic program consists of clinical conferences, journal club, and biopsy conferences.

The research areas of the 11 full-time faculty members include acid base physiology, renal transport systems, molecular biology, hypertension, dialysis, lupus nephritis, focal segmental glomerulosclerosis, and renal transplantation.