Mesangial Lupus Nephritis (WHO Class II) with Associated Nephrotic Syndrome : A Case Report and Review the Literature

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Abstract

Mesangial lupus nephritis (WHO class II) usually represents the earliest and mildest form of glomerular involvement. Nephrotic syndrome and renal insufficiency are rarely seen. Herein, we report an unusual case of an SLE patient who presented with nephrotic syndrome, active urinary sediment and azotemia. Her renal biopsy however, showed only mesangial nephritis (WHO class IIa). There are only nine similar cases reported with complete survey in the literature. Including our patient, persistent nephrotic syndrome was observed in four and morphologic transformation occurred in three of these 10 cases. These

cases altogether reinforce that lupus patients with mild mesangial nephritis may have clinical and histologic progression of renal disease, and therefore, a renal biopsy is an essential clinical tool in the therapeutic and prognostic approach to lupus nephritis.

Key Words: mesangial lupus nephritis, nephrotic syndrome

Introduction

Nephrotic syndrome in systemic lupus erythematosus (SLE) is usually associated with lesions classified as diffuse proliferative or membranous nephritis (World Health Organization [WHO] class IV or V). Patients with mesangial lupus nephritis (WHO Class II) typically have inactive urinary sediment, mild proteinuria (usually < 1 g daily), an unremarkable level of serum creatinine, and a normal glomerular filtration rate (GFR) [1]. It is rare for class II lupus patients to have a significantly elevated serum creatinine, and nephrotic range proteinuria (>3 g daily) is found only in case report. In this article, we report on a patient with class II disease with nephrotic range proteinuria, active urinary sedement and azotemia and review the literature on this topic.

Case Report

A 19-year-old girl without a significant past medical history was admitted to our hospital because of a several-day history of progressive swelling of the face and legs in July of 1997. Preceding upper respiratory infection with productive cough had bothered her for about 10 days before admission. She had no urinary complaints, gross hematuria, fever, or flank pain. Physical examination revealed moderate pretibial edema and puffy eyelids. Nephrotic syndrome with proteinuria (8.12 g/d), active urinary sediment, mild azotemia, and hypocomplementemia (C3, 51 mg/dl; C4, 20 mg/dl) were present at admission (Table 1). Her blood pressure was 100/70. The urinalysis showed 25-30 RBCs/HPF and 35-50 WBCs/HPF.

Other laboratory results were as follows: antinuclear antibody, 640X+; RA factor, <20.0 IU/ml (normal, <30 IU/ml); total hemolytic complement (CH50), 13.7 U/ml (normal 32.6-39.8 U/ml); 24hr creatinine clearance, 52.2 ml/min; positive LE cell; anti double-stranded DNA (-) and anti-streptolysin O titer, 42.9 IU/ml (normal, 166-250 IU/ml). There was no anemia, but lymphopenia (lymphocytes, 546/mm^3) was found.

A percutaneous renal biopsy performed one week after admission

showed minimal glomerular changes on light microscopy. Immunofluorescence microscopy revealed minimal deposition of IgG and C3 in the mesangium. On electron microscopy, the mesangial areas contained discrete electron-dense deposits (Figure) . No cellular proliferation was present and no deposits were seen at the periphery of the glomerular capillaries. Tubulo-reticular structures were identified in the cytoplasm of endothelial cells. The overall findings were consistent with a diagnosis of mesangial lupus nephritis (WHO class IIa).

Oral prednisolone, 45 mg daily, was prescribed initially. She received one course of prednisolone therapy but in vain. Heavy proteinuria still persisted later. She moved to Southern Taiwan at that time.

One year later, she was admitted for evaluation of abdominal pain and poor appetite in a hospital in Southern Taiwan. An impression of mesenteric vasculitis was made by abdominal computed tomographic imaging scanning. Intravenous pulse methylprednisolone was given and the patient showed a good response. After discharge, the nephrotic syndrome improved well as the edema subsided and her albumin level increased to 3.6 gm/dl. The prednisolone was then decreased in the clinic to 5 mg/d in January of 1999 (Table 1).

Discussion

A diagnosis of systemic lupus erythematosus (SLE) is made based on fitting five criteria for SLE including renal disorder, ANA 640X+, lymphopenia less than 1500 / mm^3, positive LE cells, and a butterfly rash that was observed in late 1997 [10].

In this article, we report on a patient with SLE, nephrotic range proteinuria, active urinary sediment and azotemia in whom the renal biopsy unexpectedly revealed only a mesangial lesion. It should be addressed that nephrotic syndrome and renal insufficiency are rarely seen in patients with mesangial lupus nephritis (class II). To our knowledge, there are only nine similar cases reported with complete survey in the literature. These cases as well as our own are summarized in Table 2 [2-9].

The mesangial immune deposits, the endothelial tubulo-reticular inclusions, and the clinical setting of this patient suggested the diagnosis of class II lupus nephritis. The pathogenesis of nephrotic syndrome with mesangial nephritis is poorly understood but if has been speculated that immune complex deposits in the mesangium lead to the release of cytokines, which alter glomerular permeability [9].

Monitoring proteinuria may not be a predictable marker of the response to therapy. Although protein excretion frequently falls, healing of the inflammatory process is often associated with permanent glomerular scarring, leading to some degree of irreversible proteinuria [11]. Increasing protein excretion and active urinary sediment usually reflect ongoing active disease. The level of anti-DNA antibody and the total serum hemolytic complement activity remain to be the two most useful measures of disease activity [1]. In our case, although moderate proteinuria (1.24 g/d) was still present in January of 1999, the nephrotic syndrome subsided and the level of anti-ds DNA dropped to 40X+ after prednisolone therapy. Unfortunately, active urinary sediment and increasing urinary protein (2.03 g/day) recurred when an attempt was made to taper prednisolone therapy in April of 1999 (Table 1). The urinalysis revealed 25-30 RBCs/HPF and 13-16 WBCs/HPF at that time.

The optimal therapeutic approach for a mesangial lupus patient with nephrotic syndrome remains to be established. However, we favor reserving aggressive immunosuppression for those patients with more severe manifestations of nephrotic syndrome. In this regard, some studies found that the addition of cyclophasphamide to corticosteroids

lowered the incidence of progression to end-stage renal disease by 40% compared to therapy with corticosteroids alone [1,12]. In this young girl, we should be aware of the complications such as infertility, infection, and malignancy. Cyclophosphamide may be both more effective and less toxic when given as monthly intravenous boluses of 0.5-1.0 gm/sq m of body surface area in a saline solution over 30 to 60 minutes. A possibly safer alternative than cyclophosphamide in this girl is oral azathioprine (2 mg/kg/day), which has a much lower risk of late neoplasia and little risk of ovarian dysfunction. Espinoza et al. suggested that therapy with indomethacin might be beneficial for SLE patients with refractory nephrotic syndrome [8]. However, the potential side effects of indomethacin should be monitored closely. Tanaka et al reported that assaying the glucocorticoid receptor of mononuclear leukocytes in patients with lupus nephritis may provide a predictive clue for assessing responsiveness to glucocorticoid therapy [13]. Patients with primary cortisol resistance show reduced glucocorticoid receptor levels. Other modalities have been tried in patients with refractory lupus nephritis, including plasmapheresis, total lymphoid irradiation, intravenous immunoglobulin, and cyclosporine [1].

As summarized in Table 2, persistent nephrotic syndrome was

observed in cases 1, 2, 4, and 8, and morphologic transformation occurred in three of them. Among them, diffuse proliferative nephritis was found in cases 1 and 2, and membranous nephritis in case 4. This observation may imply that the development of persistent nephrotic syndrome in a patient with mesangial nephritis predicts the transformation to diffuse proliferative or membranous nephritis (WHO class IV or V). However, it is unusual for these transformations to occur very rapidly. Therefore renal biopsies need only rarely be repeated at less than six month intervals [1]. In case 8, a second kidney biopsy was done only 5 months after the first biopsy, a duration that might be too short to develop transformation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) with ibuprofen were prescribed for arthralgia in cases 4, 8, and 9, and NSAID-induced nephritis should be entertained. From this perspective, we suggest that an NSAID should not be used in nephrotic patients with SLE.

In conclusion, our case illustrates that mesangial lupus nephritis, although rarely a cause of renal insufficiency, can be associated with nephrotic syndrome and azotemia. It is clear that neither clinical nor laboratory findings are reliable in predicting the renal histological findings in SLE patients. The renal biopsy is an essential clinical tool in

the therapeutic and prognostic approach to lupus nephritis [14]. Furthermore, the fact that active urinary sediment and increasing urinary protein recurred in this patient probably portended a poor prognosis for her renal function. It is not known how best to treat a case such as this, but we should reserve aggressive immunosuppression for this patient with more severe manifestations of nephrotic syndrome. Finally, a second kidney biopsy will be considered to rule out the possibility of morphologic transformation if nephrotic syndrome recurs.

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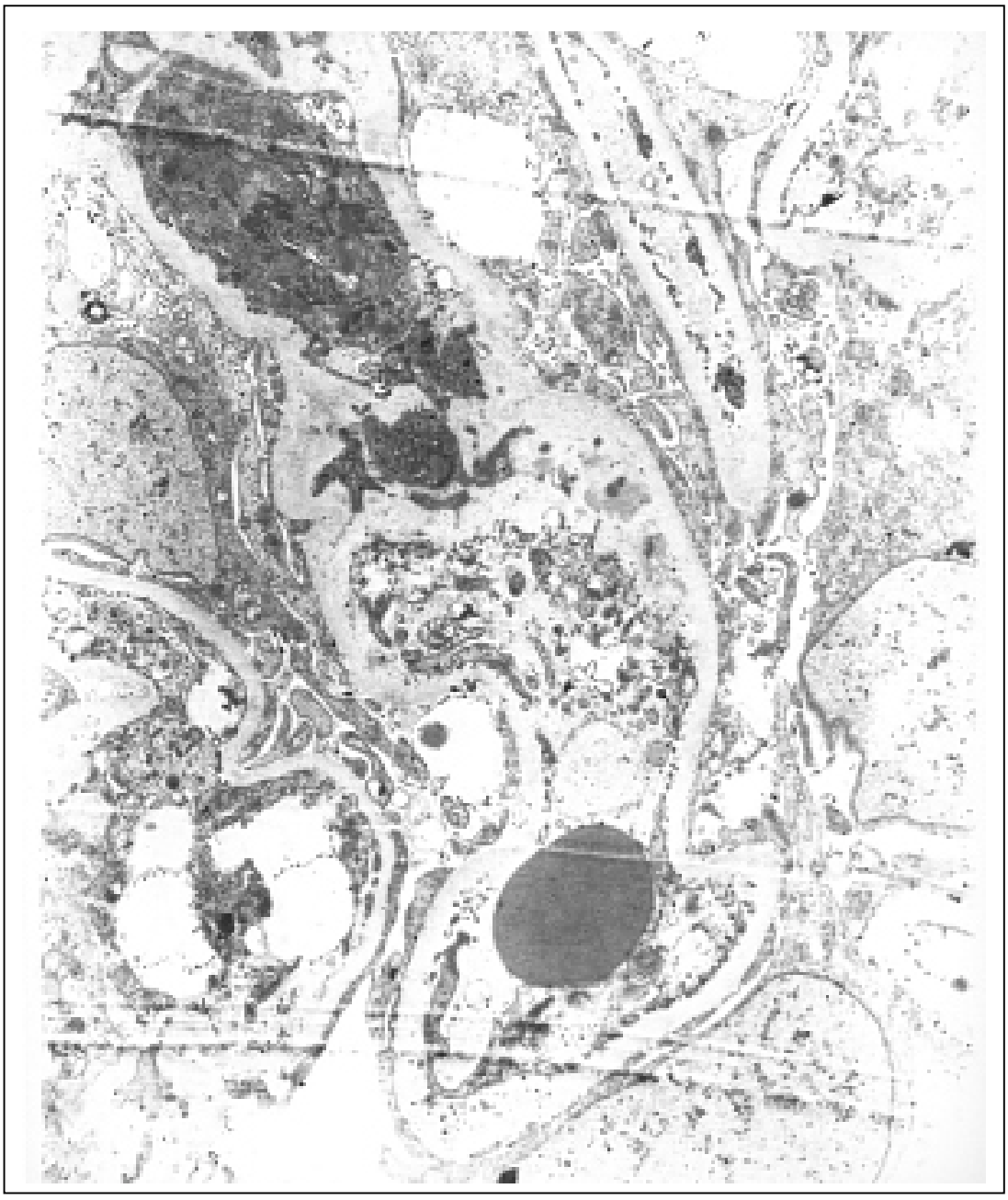

Figure : The mesangial areas contained discrete electron dense deposits.

(Electron microscopy, original magnification 3000X)

TABLE 1 : Clinical course of a patient with mesangial lupus nephritis and the nephrotic syndrome

Year	1997			1998				1999	
Month	JUL.	AUG.	NOV.	JAN.	MAY	AUG.	NOV.	JAN.	APR.
Serum values									
BUN, mg/dl	36→31	38							
Creatinine, mg/dl	0.9→2.4	1.0	0.5	0.6	0.7	0.6→1.6			
Albumin, gm/dl	0.8	1.2	2.0	2.2	1.1	1.3→1.9		3.6	
Cholesterol, mg/dl	302	524	293	458	423	293			
C3, mg/dl	51	55	60		39	32.8	79.7		
C4, mg/dl	20	19	20		15	12.5	25.5		
Anti-ds DNA	(−)	20X+	80X+		640X+	>320X+	40X+		
Urinalysis									
Protein	3+	3+	3+	3+		500mg/dl	75mg/dl	150mg/dl	500mg/dl
RBC/HPF	25-30	3-7	3-7	0-2		45-50	3-5	3-5	25-30
WBC/HPF	35-50	3-7	3-7	0-2		12-15	Negative	1-2	13-16
24hr protein, g/day	8.12			3.17				1.24	2.03
Treatment									
prednisolone, mg/d	45	45	20→5	40	40	45	20→10	5	7.5

BUN=blood urea nitrogen; C3, normal 90-150; C4, normal 17-37; RBC=red blood cells; HPF=high-power field; WBC=white

blood cells.

TABLE 2: Summary of the ten reported cases of mesangial lupus nephritis with associated nephrotic syndrome

Case number /Reference	Age/Sex (yr)	Proteinuria (g/d)	BUN/Cr (mg/dl)	Albumin (g/dl)	Treatment/Outcome
1.Baldwin et al.[2]	NA/Male	>3	NA	NA	1st biopsy: MsPGN. Nephrotic syn developed after 1 yr.. 2nd biopsy: MsPGN. Died in renal failure 1 yr later. Autopsy: DPGN.
2.Zimmermann et al.[3]	24/Female	3.9	NA	NA	1st biopsy: MsPGN. Steroid, azathioprine. 2nd biopsy 3 yr later: DPGN. After 9 mon. of steroid and azathioprine, BUN 32 mg/dl and proteinuria 2.5 g/d.
3.Abuelo et al.[4]	28/Female	6.93	14/0.7	1.8	Ten relapses occurred during 3 yr follow-up whenever prednisolone dose ≤ 15 mg/d. The 10th relapse was treated with chlorambucil. No relapse for 2 yr after.
4.Bakir et al.[5]	24/Male	12.6	NA/1.8	NA	1st biopsy: MsPGN. Steroid. Persisted nephrotic 1 yr later. 2nd biopsy: MLGN. Dependence on high-dose

					prednisone. Added IV cyclophosphamide later.
5.Trachtman [6]	18.5/Female	5	Normal	2.2	Nephrotic syndrome sponetaneously resolved 6 wk later.
6.Braun et al. [7]	27/Female	3.4	NA/10.3	NA	Coma and respiratory failure with ventilator developed. Steroid, hemodialysis, cyclophosphamide, plasma exchange. Consciousness became clear later. The renal function completely recovered dramatically.
7.Espinoza et al. [8]	28/Female	4.1	NA/0.9	3.6	Nephrotic syn for 2 yr. Prior therapy with azathioprine and prednisone. Added indomethacin 150 mg/d for 4 wk, proteinuria was 0.04 g/d, albumin 4.1 g/dl and Cr 1.2 mg/dl. No relapse occurred after 1 yr of indomethacin.
8.Srankeviciute et al. [9]	36/Female	20	61/5.0	0.7	1st biopsy: MsPGN and ATN. Steroid and cyclophosphamide. Nephrotic syn Persisted. 2nd biopsy: MsPGN. After 4 wk of cyclosporine, proteinuria 10 g/d and Cr 1.3 mg/dl.
9.Srankeviciute et al. [9]	33/Female	4.2	13/0.9	2.7	Low-does prednisone and plaquenil. After 10 mon, Cr 0.8 mg/dl and proteinuria 1.0 g/d.
10.Present case	19/Female	8.12	31/2.4	0.8	Steroid. After 18 mon, nephrotic syn subsided and albumin was 3.6 g/dl.

BUN=blood urea nitrogen; Cr=creatinine; NA=not available; MsPGN=mesangial proliferative glomerulonephritis;

DPGN=diffuse proliferative glomerulonephritis; MLGN=membranous lupus glomerulonephritis; IV=intravenous;

ATN=acute tubular necrosis; syn=syndrome; yr=year; mon=month; wk=week.