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Minimal change disease in systemic lupus erythematosus

G.K. Dube[1], G.S. Markowitz[1], J. Radhakrishnan[2], G.B. Appel[2] and V.D. D'Agati[1]

[1]Department of Pathology and [2]Department of Medicine, Columbia University, New York Presbyterian Hospital, New York, NY, USA

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Abstract. We report the clinical and pathologic findings in 7 patients with systemic lupus erythematosus and minimal change disease. All 7 patients presented with full nephrotic syndrome including peripheral edema, nephrotic range proteinuria (mean 9.6 g/day), and hypoalbuminemia (mean 1.8 g/dl). In all cases, renal biopsy revealed diffuse foot process effacement in the absence of significant peripheral capillary wall immune deposits, findings consistent with minimal-change disease. In addition, 5 cases displayed mesangial electron-dense deposits, with or without associated mesangial proliferation, consistent with underlying lupus nephritis class II. In all cases, steroid therapy induced a rapid remission of nephrotic syndrome. Minimal change disease is an underrecognized and readily reversible form of nephrotic syndrome in systemic lupus erythematosus. Because it may occur superimposed on mild mesangial proliferative lupus nephritis, this entity may be misinterpreted as an atypical presentation of lupus nephritis class II. Proper recognition of this entity requires careful integration of the renal biopsy immunofluorescence and electron microscopic findings.

Introduction

Nephrotic syndrome is a common presentation of lupus nephritis. In patients with systemic lupus erythematosus (SLE) and the nephrotic syndrome, the two most common renal biopsy findings are diffuse proliferative lupus nephritis (WHO class IV) and membranous lupus nephritis (WHO class V). Both class IV and V lupus nephritis typically present with significant proteinuria, of which 67 – 90% of class V and approximately 50% of class IV have nephrotic syndrome [Appel and Valeri 1994, Appel et al. 1978, Baldwin et al. 1977]. Focal proliferative lupus nephritis (class III) is typically associated with subnephrotic proteinuria, although up to one third of patients may present with nephrotic syndrome [Appel et al. 1978, D'Agati 1998, Magil et al. 1982]. By contrast, fewer than 50% of patients with mesangial proliferative lupus nephritis (WHO class II) manifest proteinuria which is usually mild (< 1 g/day) [D'Agati 1998]. Nephrotic syndrome is not characteristic of class II [Appel and Valeri 1994, D'Agati 1998, Ginzler et al. 1980, Le Thi Huong et al. 1999], with rare exception [Stankeviciute et al. 1997].

We report the clinical and pathologic findings in 7 patients with SLE who developed minimal change disease (MCD). In all cases, renal biopsy was essential to differentiate MCD from lupus nephritis, a distinction which played a major role in directing therapy and determining prognosis.

Methods

We reviewed all renal biopsy specimens received by the Renal Pathology Laboratory at Columbia Presbyterian Medical Center between 1986 and 2000 for the presence of MCD in the setting of SLE. Seven cases were identified. All cases were processed for light microscopy and electron microscopy; in 6 of 7 cases tissue was available for immunofluorescence (IF). Routine IF was performed on 3 m cryostat sections using polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q, , , fibrinogen, and albumin (Dako Corporation, Carpenteria, CA, USA). Immunofluorescence was graded on a scale of (0, ±, 1 – 3+).

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Correspondence to
Dr. V.D. D'Agati
Department of Pathology, Renal Path Lab,
Columbia Presbyterian Medical Center,
630 West 168th Street,
VC 14-224, New York,
NY 10032, USA
vdd1@columbia.edu

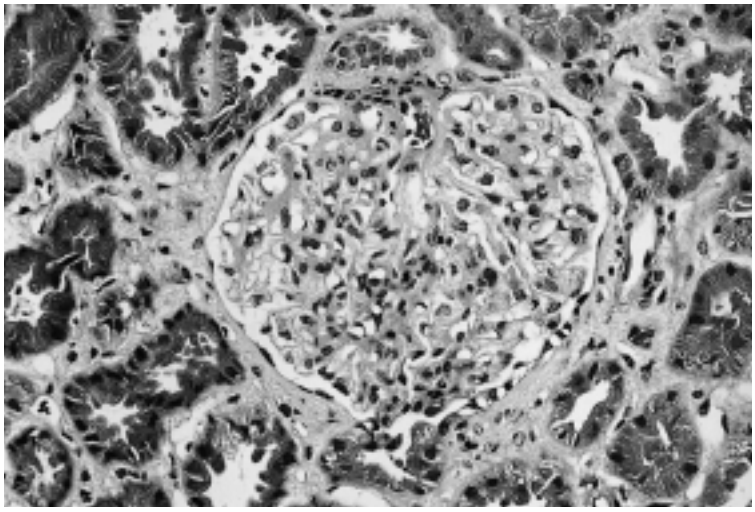

Figure 1a.

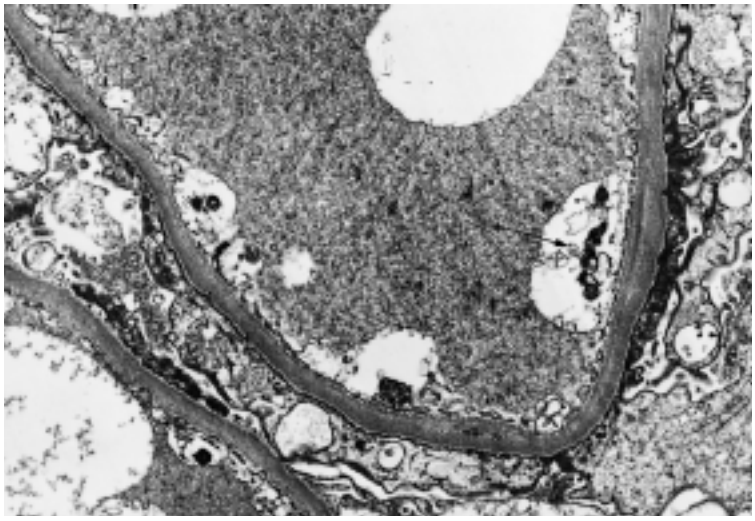

Figure 1b.

Figure 1. Renal biopsy from patient No. 4. A: Representative glomerulus shows mild segmental mesangial hypercellularity (hematoxylin and eosin, × 250). B. There is extensive effacement of foot processes. The glomerular basement membranes are otherwise unremarkable, without evidence of electron-dense deposits. A tubuloreticular inclusion is present in an endothelial cell (arrow) (electron micrograph, × 6,000).

Inclusion criteria consisted of presentation with nephrotic syndrome, fulfillment of 4 or more American Rheumatism Association (ARA) criteria for SLE [Tan et al. 1982] and renal biopsy findings of glomeruli with normal cellularity or minimal mesangial prominence and complete foot process effacement, in the absence of significant subendothelial or subepithelial deposits. In each case, a careful review of the clinical and pathologic findings was performed and data on treatment and outcome were obtained.

Results

The systemic and renal clinical parameters are summarized in Table 1. Six of 7 patients were female. The age at onset of nephrotic syndrome and renal biopsy ranged from 18 – 58 years (mean 32.7 years). All patients were ANA-positive, fulfilled at least 4 ARA criteria for SLE and presented with full nephrotic syndrome including peripheral edema, nephrotic-range proteinuria (7 – 12 g/day; mean 9.6 g/day), and hypoalbuminemia (0.6 – 2.4 g/dl; mean 1.8 g/dl). Renal insufficiency was present at the time of biopsy in 4 of 7 patients (defined as serum creatinine > 1.2 mg/dl).

Three patients used NSAIDs prior to the onset of the nephrotic syndrome. Patient No. 3 used celecoxib (Celebrex) 100 mg b.i.d. for arthralgias for 1 week prior to developing anasarca although the treating physician documented peripheral edema prior to the use of celecoxib. Patient No. 4 took ibuprofen 1,000 mg q 4 hours for an ankle injury for 1 week prior to the development of the nephrotic syndrome (far exceeding the recommended dose of 200 mg q 4 – 6 hours). Patient No. 5 was treated for arthralgias with naproxen (Naprosyn) 500 mg b.i.d. for 1 year prior to developing the nephrotic syndrome.

Following renal biopsy, all 7 patients were treated with prednisone and NSAID use was discontinued in patients 3, 4, and 5. All 7 patients subsequently experienced a remission of the nephrotic syndrome. Serum creatinine levels returned to baseline within 1 month in 3 of the 4 patients who presented with renal insufficiency (and at 6 weeks in the single remaining patient). Three patients experienced subsequent relapses of nephrotic syndrome: in patient No. 2, relapse occurred during prednisone taper and was treated with cyclosporine. Nephrotic syndrome subsequently remitted, followed by 2 later relapses. Patient No. 3 experienced relapse of nephrotic syndrome 6 months post-biopsy and repeat biopsy again documented MCD and lupus nephritis (LN) IIb. Patient No. 6 had a relapse of the nephrotic syndrome 1 year after his initial presentation and repeat biopsy revealed transformation to LN class III.

The renal biopsy findings are detailed in Table 2. Glomerular sampling for light microscopy ranged from 1 – 22 glomeruli (mean

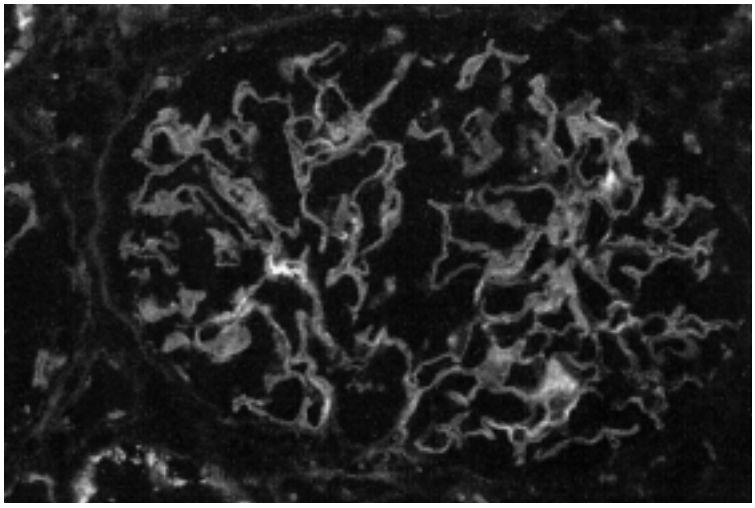

Figure 1c.

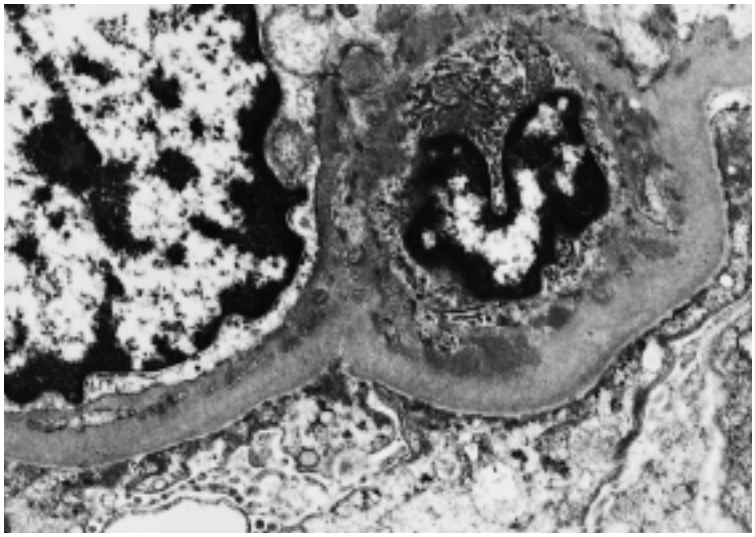

Figure 1d.

Figure 1. Renal biopsy from patient No. 4. c: Immunofluorescence staining for IgG shows sparse segmental 1+ positivity in the mesangium (× 500). d: Electron micrograph showing small paramesangial electron-dense deposits (× 8,000).

9.6); in all 7 cases, no segmentally sclerotic glomeruli were identified. Glomeruli ranged from normocellular (2 cases) to mild segmental mesangial hypercellularity (4 cases) (Figure 1a). In a single case (No. 3), moderate diffuse mesangial proliferation was seen. No biopsy had endocapillary proliferation or cellular crescents. Although tubular injury in the form of tubular simplification and interstitial edema was seen in cases with acute renal insufficiency, there was no evidence of tubular atrophy or interstitial fibrosis. Three cases displayed mild focal interstitial inflammation, without associated tubulitis.

On ultrastructural analysis, all 7 cases had extensive (90 – 100%) foot process effacement accompanied by podocyte hypertrophy and microvillous change (Figure 1b). The glomerular basement membranes were otherwise unremarkable, with the exception of an isolated minute subendothelial or subepithelial deposit in 4 cases. This combination of findings met morphologic criteria for the diagnosis of MCD.

In no case were peripheral capillary wall immune deposits detected by immunofluorescence. Five cases displayed exclusively mesangial positivity by IF. Four of the 5 cases had mesangial hypercellularity and mesangial staining for IgG, C3, and and light chains (± to 2+ intensity) with corresponding mesangial electron-dense deposits by electron microscopy (EM) (cases Nos. 1, 3, 4, 7) (Figures 1c, d). Accordingly, these 4 cases were classified as having associated lupus nephritis class IIb. In case No. 6, glomeruli were not available for immunofluorescence although rare segmental mesangial deposits were seen by EM, without associated mesangial hypercellularity, consistent with lupus nephritis class IIa. In 1 case (No. 2), there was mesangial positivity of 1+ intensity for IgM and C1 with only rare paramesangial electron densities. In the absence of co-deposits of IgG, these findings were felt to be inadequate to diagnose underlying lupus nephritis class II. No deposits were identified in case No. 5. Endothelial tubuloreticular inclusions were present in 4 of the 7 cases.

Discussion

We describe the clinical and pathologic findings in 7 patients with SLE who presented with nephrotic syndrome and were found to have MCD. In all 7 patients, nephrotic syndrome remitted following treatment with prednisone, although 3 experienced subsequent relapses.

Renal biopsy from all 7 patients revealed diffuse podocyte changes and complete foot process fusion, consistent with MCD. In 5 patients, biopsy also revealed mesangial deposits, consistent with underlying lupus nephritis class IIa or IIb. These 5 patients with MCD

Table 1. Clinical findings in patients with SLE and MCD.

Case	1	2	3	4	5	6	7
Age (years)	43	28	32	18	58	20	30
Race	African-American	White	Hispanic	Hispanic	White	White	Hispanic
Gender	Female	Female	Female	Female	Female	Male	Female
Anti-nuclear antibodies (ANA)	positive (1 : 640)	positive	positive (1 : 640)	positive	positive	positive	positive
Anti-DNA antibodies	negative	positive	positive	positive	positive	positive	positive
ARA criteria	1. ANA 2. Malar rash 3. Anemia 4. LN IIb	1. ANA 2. Anti-DNA Ab 3. Pericarditis 4. Lymphopenia	1. ANA 2. Anti-DNA Ab 3. Arthritis 4. Lymphopenia 5. LN IIb	1. ANA 2. Anti-DNA Ab 3. Arthritis 4. Anemia 5. LN IIb	1. ANA 2. Anti-DNA Ab 3. Arthritis 4. Pleuritis	1. ANA 2. Anti-DNA Ab 3. Arthritis 4. Thrombocytopenia 5. LN IIa	1. ANA 2. Anti-DNA Ab 3. Arthritis 4. Serositis 5. LN IIb
Antecedent NSAID use	no	no	Celecoxib 100 mg b.i.d. for 1 week	Ibuprofen 1,000 mg q 4 h for 1 week	Naproxen 500 mg b.i.d. for 1 year	no	no
Edema	yes	yes	yes	yes	yes	yes	yes
Blood pressure (mmHg)	“elevated”	120/70	170/110	132/90	138/75	130/70	130/84
24-hour urine protein (g/day)	11.44	7	“nephrotic-range”	12	8.9	11.9	6.5
Serum albumin (g/dl)	1.9	2.4	2.2	0.6	2.0	1.9	1.7
Serum cholesterol (mg/dl)	NA	507	270	327	263	NA	NA
Serum creatinine (mg/dl)	1.6	0.8	0.8	1.2	2.9	2.8	2.6
Hypocomplementemia	no	NA	no	yes	no	yes (mild)	NA
Urine RBCs	5 – 10/hpf	no	no	“rare”	no	yes	5 – 10/hpf
Treatment	prednisone	prednisone	prednisone D/C celecoxib	prednisone D/C ibuprofen	prednisone D/C naproxen	prednisone	prednisone
Time to initial follow-up	1 month	8 months	2 months	2 weeks	1 month	2 weeks	6 weeks
Initial follow-up	sCr 1.1 mg/dl Uprot:creat 1.5	sCr 0.5 mg/dl 24 h prot 400 mg	24 h prot 1.2 gm	sAlb 2.7 g/dl 15 lb weight loss	sCr 1.0 mg/dl 24 h prot 300 mg	sCr 1.0 mg/dl 24 h prot 600 mg	sCr 0.7 mg/dl 2+ protein on UA

Key: ARA = American Rheumatism Association, LN = lupus nephritis, NSAID = non-steroidal anti-inflammatory drug, NA = not available, D/C = discontinue, UA = urinalysis.

Table 2. Renal biopsy findings in patients with SLE and minimal change disease

Case	1	2	3	4	5	6	7
Light Microscopy							
# glomeruli	1	13	5	10	22	4	12
# sclerotic gloms	0	0	0	0	1	0	0
Appearance of glomeruli	mild MP	mild MP	moderate MP	mild MP	nl	nl	mild MP
Tubular atrophy	NA	0	0	0	0	0	0
Interstitial fibrosis	NA	0	0	0	0	0	0
Interstitial inflammation	NA	0	mild	0	mild	mild	0
Vascular disease	NA	0	0	0	mild	mild	0
Immunofluorescence							
Mesangial deposits	2+ IgG/C3/K/L	1+ IgM/C1	1+ IgG/IgM/IgA/C3/K/L	IgG/IgM/C3/K/L	0	NA	IgG
GBM deposits	0	0	0	0	0	NA	0
TBM deposits	0	0	0	0	0	NA	0
Interstitial deposits	0	0	0	0	0	NA	0
Vascular deposits	0	0	0	0	0	NA	0
Electron Microscopy							
Mesangial deposits	2+ global	1+ segm	1+ global	1+ segm	0	1+ segm	2+ global
GBM deposits	rare SN/SP	0	rare SN	0	0	rare SN/SP	rare SP
TBM deposits	0	0	0	0	0	0	0
Interstitial deposits	0	0	0	0	0	0	0
Vascular deposits	0	0	0	0	0	0	0
Endothelial TRIs	0	0	3+	3+	0	3+	2+
% Foot process fusion	95	95	95	90	95	100	100
Final diagnosis	LN IIb/MCD	MCD	LN IIb/MCD	LN IIb/MCD	MCD	LN IIa/MCD	LN IIb/MCD

Key: MP = mesangial proliferation, nl = normal, NA = not assessable/not applicable, GBM = glomerular basement membrane, TBM = tubular basement membrane, segm = segmental, SN = subendothelial, SP = subepithelial, TRI = tubuloreticular inclusions, LN = lupus nephritis, MCD = minimal change disease

and lupus nephritis class II displayed subtle clinical differences from the 2 patients with MCD alone, including hypertension in 3, microscopic hematuria in 4 and hypocomplementemia in 2. The presence in 4 patients of renal insufficiency that rapidly resolved following treatment with prednisone is typical of adult-onset MCD [Falk et al. 2000]. None of the patients had evidence of associated acute interstitial nephritis on renal biopsy.

By definition, the pathologic lesions of class II lupus nephritis are limited to the mesangium. The relationship of isolated mesangial disease to proteinuria is not clear. Mesangial cells may release and respond to autocrine and paracrine substances that can lead to alterations of the glomerular filtration barrier and mild, subnephrotic proteinuria [Savin 1993]. The isolated mesangial changes seen in the 5 patients with MCD and lupus nephritis class II appear insufficient to account for the complete foot process fusion and full nephrotic syndrome, supporting a diagnosis of superimposed MCD. This conclusion is further supported by the rapid and complete response to steroids alone (within 1 month in 4 of 7 patients). This superimposition of 2 conditions is analogous to the occurrence of MCD in patients with mesangial proliferative IgA nephritis. In both situations, the immune complex load, which is restricted to the mesangium, is inadequate to explain the diffuse podocyte injury and heavy proteinuria [Clive et al. 1990]. This entity must also be differentiated from rare examples of "pauci-immune" lupus nephritis in which there is little or no immune staining despite the presence of active proliferative nephritis [Akhtar et al. 1994].

MCD accounts for 10 – 15% of cases of primary nephrotic syndrome in adults, and by definition, virtually all patients present with nephrotic syndrome [Falk et al. 2000]. Up to 9% of cases of adult-onset MCD have been linked to NSAID use [Abraham and Keane 1984, Feinfeld et al. 1984, Warren et al. 1989]. Patients with NSAID-associated MCD often display concurrent features of in-

terstitial nephritis and may present with significant renal insufficiency [Whelton 1999].

NSAIDs are commonly prescribed for the treatment of clinical manifestations of lupus, including fever and arthritis [Kimberly 1988, Sims and Smith 1996]. One survey of 12 university-based rheumatologists revealed that among 925 lupus patients, 84% had used NSAIDs subsequent to their development of SLE [Wallace et al. 1989]. Although to date there are no reports of MCD associated with cyclooxygenase (COX)-2-selective inhibitors, current evidence suggests that COX-2-selective NSAIDs have similar renal effects as non-selective NSAIDs [Brater 1999].

Among the 7 patients in our cohort, 3 had a history of NSAID use prior to the development of MCD, including non-selective NSAIDs in 2 and celecoxib (a COX-2-selective NSAID) in 1 patient. Two of the patients (patients Nos. 3 and 4) used NSAIDs for 1 week prior to presentation, a period of treatment that is far shorter than that typically reported for NSAID-associated MCD [Whelton 1999]. NSAID-associated MCD is particularly unlikely in patient No. 3, because of the presence of lower extremity edema prior to use of the COX-2-selective NSAID. Despite the short course of ibuprofen in patient No. 4, we cannot exclude an NSAID effect given the large doses received. The rapid remission of the nephrotic syndrome in each of the 3 patients in response to prednisone and NSAID withdrawal would be consistent with either idiopathic or NSAID-associated MCD.

There are a few case reports in the English literature of MCD in SLE. Makino et al. [1995] described a 41-year-old female with SLE and nephrotic syndrome in whom renal biopsy demonstrated MCD but no evidence of lupus nephritis. Nishihara et al. [1997] detailed a 17-year-old female with MCD which responded to prednisolone and was followed 7 months later by the development of SLE. Perakis et al. [1998] reported a 45-year-old female with history of SLE and lupus nephritis class III, who at the time of repeat biopsy 5 years later had nephrotic syndrome and changes consistent with MCD. In all 3 cases, the nephrotic syndrome was at least initially responsive to steroids and in all 3 reports, NSAID use was not described. Additional rare cases of MCD in the setting of SLE have been reported in the Japanese literature [Horita et al. 1997, Matsumura et al. 1989, Okai et al. 1992].

Previous reports of patients with lupus nephritis class IIb presenting with full nephrotic syndrome are likely to represent unrecognized examples of this entity. Stankeviciute et al. [1997] described 2 patients with nephrotic syndrome and biopsy findings of class II lupus nephritis. The first patient developed nephrotic syndrome coincident with the rapid onset of SLE. Renal biopsy demonstrated 50% foot process fusion and rare mesangial electron-dense deposits, findings interpreted as mild class II lupus nephritis. The nephrotic syndrome persisted despite treatment with corticosteroids and subsequent cyclophosphamide. Five months later, renal biopsy revealed 80% foot process fusion and the absence of electron-dense deposits, a clinicopathologic picture more consistent with MCD [Nolasco et al. 1986]. The second patient presented with nephrotic syndrome 3 months after clinical diagnosis of SLE, and following 3 months of treatment with prednisone, hydroxychloroquine and indomethacin. Renal biopsy revealed 60% foot process fusion, few mesangial deposits and a normal-appearing GBM, leading to a diagnosis of mild class II lupus nephritis [Stankeviciute et al. 1997]. On reinterpretation, the extensive foot process fusion and 3-month history of indomethacin treatment strongly suggest the possibility of NSAID-induced MCD.

MCD is an underrecognized and highly reversible form of nephrotic syndrome in patients with SLE. In this setting, renal biopsy is an essential diagnostic tool to differentiate lupus nephritis from MCD, a differential diagnosis that carries important therapeutic implications. Whereas steroids are the mainstay of treatment for MCD, in the case of lupus nephritis class II it is general practice not to direct immunosuppressive therapy specifically to the nephritis but rather to the active extrarenal manifestations of lupus [Appel and Valeri 1994]. Proper interpretation of the biopsy findings requires, above all, careful integration of the immunofluorescence and electronmicroscopic findings. The diagnosis of MCD should be considered in any patient with SLE, full nephrotic syndrome, and renal biopsy findings of lupus nephritis Class II with extensive foot process fusion.

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