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Pathologic differentiation between lupus and nonlupus membranous glomerulopathy

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Pathologic differentiation between lupus and nonlupus membranous glomerulopathy. The following clinical and pathologic features were evaluated in 170 patients with electron microscopically documented membranous glomerulopathy: age, sex, race, American Rheumatism Association lupus criteria, serum ANA, serum complement, glomerular hypercellularity, stage of subepithelial dense deposits, endothelial tubuloreticular inclusions, tubular basement membrane deposits, tissue ANA, glomerular deposition of IgG, IgM, IgA, C3, C4, and C1q. At the time of biopsy 148 patients had no clinical evidence for lupus, and 22 had a clinical diagnosis of lupus. Six additional patients eventually developed overt lupus after an average of 12 months. Incidences of serologic and pathologic features in lupus as compared with nonlupus membranous glomerulopathy were determined. These data were used to calculate sensitivity, specificity, positive and negative predictive values, and overall efficiency of each parameter in differentiating between lupus and nonlupus membranous glomerulopathy. In general, serologic, morphologic and immunohistopathologic features are more accurate at ruling out lupus than making the diagnosis of lupus. However, a number of features are significantly more frequent in lupus membranous glomerulopathy. Therefore, identification of these features, especially more than one, warrants a high suspicion of lupus rather than nonlupus membranous glomerulopathy even in patients without clinically overt systemic lupus erythematosus. The positive/negative predictive values of some of the pathologic features studied are as follows: mesangial dense deposits 63/99, subendothelial dense deposits 77/93, tubuloreticular inclusions 61/96, intense C1q deposition 47/95, tubular basement membrane deposits 100/87, and glomerular hypercellularity 26/86.

Différentiation pathologique entre glomérulopathie extra-membraneuse lupique et non lupique. Les caractéristiques cliniques et pathologiques suivantes ont été évaluées chez 170 malades atteints de glomérulopathie extra-membraneuse documentée par microscopie électronique: l'âge, le sexe, la race, les critères de lupus de l'American Rheumatism Association, les ANA sériques, le complément sérique, l'hypercellularité glomérulaire, le stade des dépôts denses sous-épithéliaux, les inclusions endothéliales tubuloréticulaires, les dépôts dans la membrane basale tubulaire, les ANA tissulaires, les dépôts glomérulaires d'IgG, IgM, IgA, C3, C4, et C1q. Au moment de la biopsie, 148 malades n'avaient pas d'argument clinique pour un lupus, et 22 avaient un diagnostic clinique de lupus. Six malades supplémentaires ont développé un lupus patent après une moyenne de 12 mois. L'incidence des caractéristiques sérologiques et pathologiques dans la glomérulopathie extra-membraneuse lupique ou non lupique a été déterminée. Ces données ont été utilisées pour calculer la sensibilité, la spécificité, les valeurs prédictives positives et négatives, et l'efficacité globale de chaque paramètre pour différencier entre glomérulopathie extramembraneuse lupique ou non lupique. D'une façon générale, les caractéristiques sérologiques, morphologiques et immunohistopathologiques sont plus puissantes pour éliminer le lupus que pour faire le diagnostic de lupus. Cependant, un certain nombre de caractéristiques sont significativement plus fréquentes dans la glomérulopathie extra-membraneuse lupique. C'est pourquoi la mise en évidence de ces caractéristiques, surtout s'il y en a plus d'une, apporte une forte suspicion de glomérulopathie extra-membraneuse plus lupique que non lupique, même chez des malades sans lupus erythémateux disséminé cliniquement patent. Les valeurs prédictives positives/négatives de certaines des caractéristiques pathologiques étudiées sont les suivantes: dépôts denses mésangiaux 63/99, dépôts denses sous-endothéliaux 77/93, inclusions tubuloréticulaires 61/96, dépôts intenses de C1q 47/95, dépôts dans la membrane basale tubulaire 100/87, et hypercellularité glomérulaire 26/86.

The characteristic light, immunofluorescence, and electron microscopic features of membranous glomerulopathy (MG) have been described thoroughly [1]. That MG occurs as one variant of lupus nephritis is also well recognized [2]. In a patient with clinically diagnosed systemic lupus erythematosus (SLE), identification of MG in a renal biopsy is presumed to indicate a common pathogenesis for the MG and SLE, thus leading to a diagnosis of lupus MG (LMG).

Certain pathologic features are known to occur more frequently in LMG than in nonlupus MG (NLMG) [3]. However, when these pathologic features suggesting LMG occur in a patient with no clinical diagnosis of SLE, how accurately can they identify those patients with unrecognized or nascent SLE? To address this question, we determined how often selected serologic, morphologic or immunohistopathologic features were present in patients with MG who had *(1)* no clinical diagnosis of SLE; *(2)* a diagnosis of SLE made at some interval after biopsy or; *(3)* a diagnosis of SLE made during or before the hospital admission when the biopsy was performed. The features studied were serum antinuclear antibodies (ANA), hypocomplementemia, glomerular hypercellularity, mesangial dense deposits, subendothelial dense deposits, endothelial tubuloreticular inclusions, tubular basement membrane deposits, biopsy tissue ANA reaction, and glomerular deposition of IgG, IgA, IgM, C3, C4, and C1q. These data were then used to calculate the sensitivity, specificity, positive predictive value, negative predictive value and overall efficiency of each serologic, morphologic, or immunohistopathologic feature in discriminating between NLMG and LMG.

Methods

Case selection. The working definition of MG used required the ultrastructural identification of regularly distributed sub-

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epithelial dense deposits (or their stage 3 or 4 intramembranous variants) without large subendothelial deposits. Unlike some definitions of LMG that would relegate a MG patient with any subendothelial deposits to a category of proliferative lupus nephritis [4], small subendothelial deposits (Fig. 1) did not exclude a patient from our MG series. And, in fact, most MG patients with small subendothelial deposits had no glomerular hypercellularity. Since the value of glomerular hypercellularity in differentiating between LMG and NLMG was to be evaluated, this feature did not exclude a MG patient either. However, patients with regularly distributed subepithelial deposits and conspicuous subendothelial deposits were excluded from the study. These patients often had diffuse hypercellularity and characteristics of either diffuse proliferative, mixed membranous and proliferative, or type 3 membranoproliferative glomerulonephritis.

A total of 170 patients were studied. Although some patients had repeat biopsies, only data from the first biopsy specimen were used for compilation. One hundred forty-eight patients found to have MG had no clinical diagnosis of SLE made before or during the hospital admission when the biopsy was performed. We evaluated followup clinical data on 78 of these patients for an average of 25 months per patient (range, 4 to 92 months). Six of these 78 patients subsequently had SLE recognized clinically after an average followup of 12 months. Twenty-two patients had a clinical diagnosis of SLE made before or during the hospital admission when the biopsy was performed.

Clinical data sought on all patients at the time of biopsy and during followup included age, sex, number of American Rheumatism Association SLE criteria [5] observed, serum ANA, and serum C3 level. By definition, all MG patients included in this study had ultrastructural examination of glomeruli, 95% had adequate glomeruli (10 or more) for light microscopic evaluation, and 84% had glomeruli examined by immunofluorescence microscopy.

Pathologic evaluation. Renal tissue samples for light microscopy were fixed in either buffered formalin or Helly's fixative. Hematoxylin and eosin, periodic acid-Schiff and Jones' silver methenamine stains were used routinely, and a Masson trichrome stain was also often used. For immunofluorescence microscopy, tissue was either snap-frozen in liquid nitrogen or held in Michel's solution [6] prior to snap-freezing. Cryostat sections were reacted with fluorescein-labeled goat or rabbit antibodies specific for human IgG, IgA, IgM, C3, C4, or C1q (Meloy Laboratories, Springfield, Virginia, or Calbiochem-Behring, LaJolla, California) and viewed with a Leitz Orthoplan or Dialux 20 microscope equipped for incident light fluorescence microscopy. Tissue samples for electron microscopy were placed either in 2.5% phosphate-buffered glutaraldehyde and postfixed in osmium tetroxide or primarily fixed in osmium tetroxide. Epon 812 thin sections stained with lead citrate and uranyl acetate were examined with a JEOL T-7 transmission electron microscope.

Glomerular hypercellularity was evaluated independently by two of the authors without knowledge of clinical, ultrastructural, or immunohistologic data. The few discordant opinions were resolved by review. Very slight focal segmental mesangial cell clustering was not designated hypercellularity. The initial ultrastructural examination of all cases was performed by one of the authors. In all patients the presence of endothelial tubuloreticular inclusions and the locations of dense deposits were expressly sought and recorded in electron micrographs. To be designated mesangial, electron dense deposits had to be internal to a recognizable paramesangial basement membrane (Fig. 1). This requirement was to prevent mistaken identification as mesangial deposits tangentially cut subepithelial deposits or subepithelial deposits on a majority of cases, one of the authors evaluated contiguous capillary loops (Fig. 2). In a majority of cases, one of the authors evaluated the initial immunofluorescence microscopic preparations, and in all other cases from which immunofluorescence microscopic data were used, recuts from the −70°C stored blocks were examined by the same author. The degree of immunofluorescence was quantitated from 0 to 4+.

Statistical analysis. To evaluate the diagnostic accuracy of pathologic differentiation between LMG and NLMG the methods of Galen and Gambino [7] were applied. A determination was designated a true positive (TP) if positive in a LMG patient, a false positive (FP) if positive in a NLMG patient, a true negative (TN) if negative in a NLMG patient, and a false negative (FN) if negative in a LMG patient. The sensitivity (SN) of a parameter is the incidence of TP results in LMG patients [(TP) ÷ (TP + FN) × (100)] and is therefore equivalent to the incidence of a given feature in LMG patients. The specificity (SP) is the incidence of TN results in NLMG patients [(TN) ÷ (TN + FP) × (100)]. The positive predictive value (PPV) is the percent positive results that are true positives in the total population of MG patients [(TP) ÷ (TP + FP) × (100)]. The negative predictive value (NPV) is the percent negative results that are true negatives in the total population of MG patients [(TN) ÷ (TN + FN) × (100)]. The overall efficiency (EFF) for differentiating between LMG and NLMG is the percent of all results that are true results, whether positive or negative [(TP + TN) ÷ (TP + FP + FN + TN) × (100)].

Results

Clinical data. The clinical data comparing the LMG and NLMG patient groups are presented in Table 1. At the time of biopsy, NLMG patients had a mean age of 42 (range, 8 to 78) and a male to female ratio of 2:1. LMG patients had a somewhat lower mean age of 30 (range, 9 to 64) and a reversal of the male to female ratio to 1:4. Eighty-seven percent of LMG were black while only 26% of NLMG patients were black. Ninety-one percent of the NLMG patients had no more than one American Rheumatism Association SLE criterion, whereas 96% of the LMG patients had four or more criteria identified at the time a clinical diagnosis of SLE was made. LMG patients with a delayed diagnosis of SLE (latent SLE) had no more than two SLE criteria at the time of biopsy, but all had four or more by the time a diagnosis of SLE was made.

Serologic data. Hypocomplementemia was rare in NLMG patients (2%) but was present in a majority of LMG patients (65%) with overt LMG patients having a higher incidence (75%) than latent LMG patients (33%). Although ANA were observed in a few NLMG patients (7%), 100% of LMG patients had ANA at the time a diagnosis of SLE was made. At the time of biopsy, 67% of latent LMG patients had ANA.

Morphologic data. Selected light and electron microscopic data are presented in Table 2. Although glomerular hypercellularity was approximately twice as frequent in LMG (27%) compared to NLMG (15%), the difference was not statistically significant ($P > 0.1$). Two NLMG patients with substantial hypercellularity (Fig. 3) but no mesangial or subendothelial deposits and no C1q or IgA by immunofluorescence microsco-

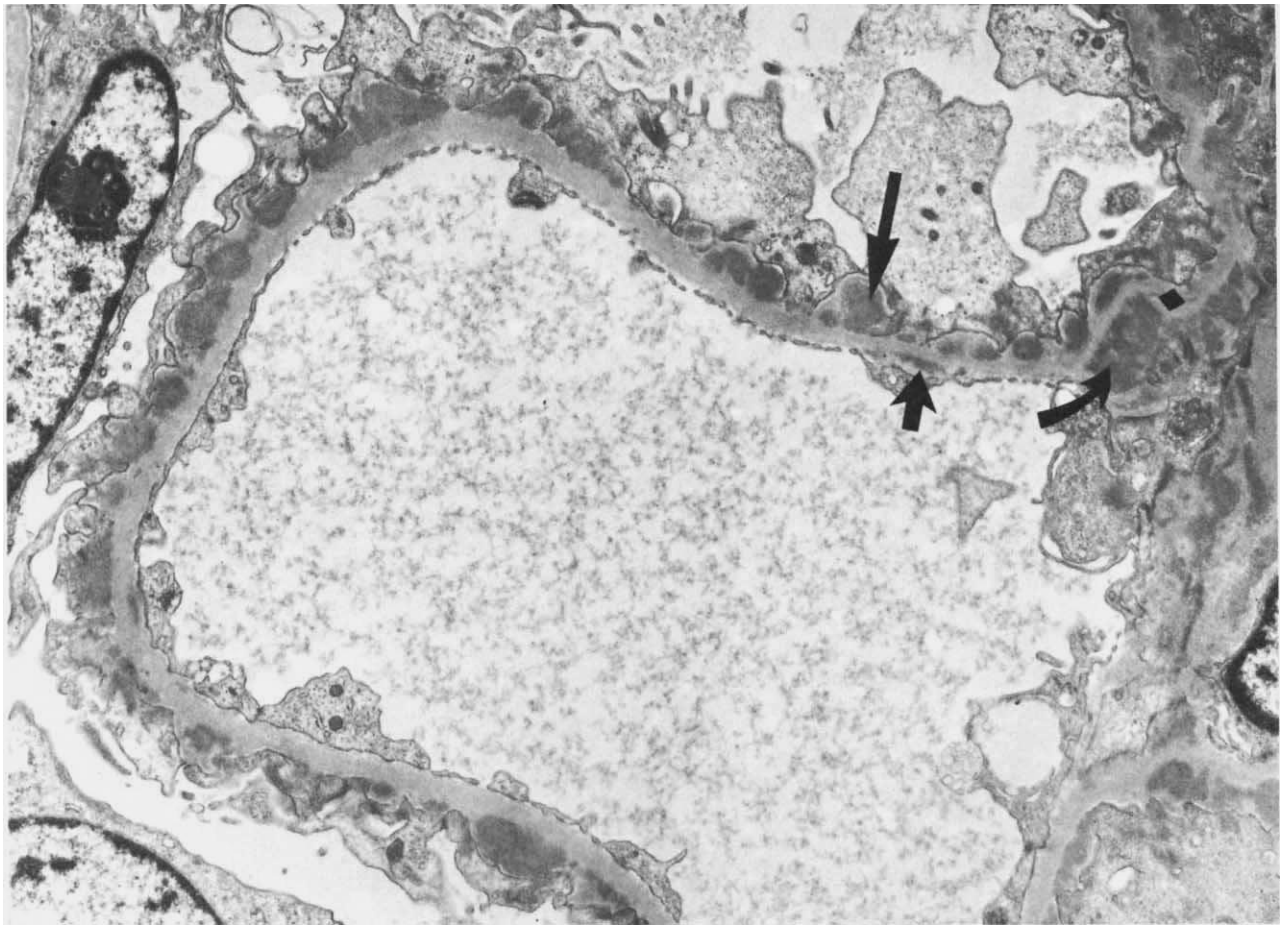

Fig. 1. *Electron micrograph of a glomerular capillary from a patient with lupus membranous glomerulopathy.* Numerous subepithelial electron dense deposits *(long straight arrow),* small subendothelial electron dense deposits *(short arrow)* and mesangial deposits *(curved arrow)* subjacent to the paramesangial basement membrane *(diamond)* are present. (×4,000)

py had repeat biopsies after 25 and 22 months, respectively, showing the same pathologic features but still no clinical evidence for SLE. Focal crescent formation and/or focal segmental sclerosis were present in a few MG patients (3.5 and 4%, respectively) but were not useful in distinguishing between LMG and NLMG. One patient with NLMG with crescents had simultaneous anti-GBM mediated injury [8]. There was no difference in the frequency of ultrastructural stages [1] of dense deposits between NLMG and LMG. Mesangial dense deposits, small subendothelial dense deposits, tubuloreticular inclusions (Fig. 4) and tubular basement membrane deposits (Fig. 5) all had a statistically significant ($P < 0.001$) greater incidence in LMG than NLMG patients. When present, tubuloreticular inclusions were more conspicuous in LMG than NLMG. All of these ultrastructural features were more frequent in overt than latent LMG patients.

Immunohistopathologic data. Renal cortical tissue samples were examined by immunofluorescence microscopy for glomerular IgG, IgM, IgA, C3, C4, and C1q. In almost all MG patients IgG was the most intensely staining Ig, and only very rarely was C3 more intense than IgG. In some LMG patients C1q staining was equal to or greater than IgG staining in intensity. All patients had diffuse global granular capillary wall deposits but rare cases had segmentally variable capillary wall deposits. A few patients, most often LMG patients, had different patterns of staining with different antisera, for example, mesangial IgM with capillary wall IgG. One patient with LMG had 3+ capillary wall staining for IgG (4+ IgG4; no IgG1, IgG2, or IgG3) but no capillary complement, and exclusively mesangial staining for

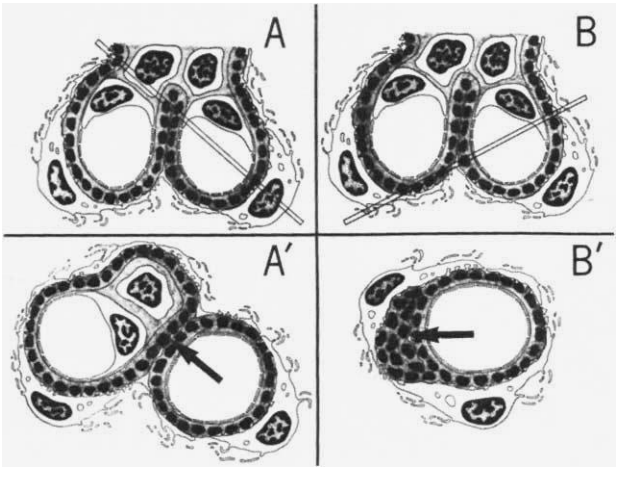

Fig. 2. *Diagram illustrating two different planes of section* (open bars in **A** and **B**) *through two adjacent glomerular capillaries that would result in ultrastructural semblances to electron dense deposits within mesangial matrix* (arrows in **A′** and **B′**) *although their true location was subepithelial.*

Table 1. Clinical data from lupus and nonlupus membranous glomerulopathy patients

Group	Mean age *range*	Sex ratio *M:F*	SLE criteria[a]	Decreased serum C3	Serum ANA
Nonlupus membranous glomerulopathy (N = 142)	42 (8 to 78)	2:1	8% 0 83% 1 8% 2	2%	7%
Lupus membranous glomerulopathy (N = 28)	30 (9 to 64)	1:4	4%[b] 3 57% 4 25% 5 7% 6 7% 7	65%	100%[b]
Overt lupus membranous glomerulopathy (N = 22)	29 (10 to 64)	1:6	5% 3 59% 4 18% 5 9% 6 9% 7	75%	100%
Latent lupus membranous glomerulopathy (N = 6)	32 (9 to 50)	1:1	33/0%[c] 0 33/0% 1 33/0% 2 0/50% 4 0/50% 5	33%	67/100%[c]

[a] The number of American Rheumatism Association criteria is cited.
[b] Percentage recorded at the time of clinical SLE diagnosis.
[c] Percentage recorded at the time of biopsy/at the time of clinical SLE diagnosis.

Table 2. Morphologic data from lupus and nonlupus membranous glomerulopathy specimens

Group	Glomerular hypercellularity	EM stage	Mesangial deposits	Small subendothelial deposits	Tubuloreticular deposits	TBM[a] deposits
Nonlupus membranous glomerulopathy (N = 142)	15%	18% I 64% II 12% III 6% IV	11%	3%	10%	0%
Lupus membranous glomerulopathy (N = 28)	27%	14% I 68% II 18% III 0% IV	96%	61%	79%	32%
Overt lupus membranous glomerulopathy (N = 22)	35%	14% I 68% II 18% III 0% IV	100%	73%	82%	35%
Latent lupus membranous glomerulopathy (N = 6)	0%	17% I 67% II 17% III 0% IV	83%	17%	67%	20%

[a] Tubular basement membrane deposits were identified by electron or immunofluorescence microscopy.

C3, C4, C1q, and IgM. One NLMG patient with mesangial dense deposits and hypercellularity had exclusively capillary wall IgG and exclusively mesangial IgA. Table 3 details the incidence of positive staining in LMG and NLMG patients. The incidence of glomerular IgG, IgM, C3, and C4 deposition was not significantly different ($P > 0.1$) between LMG and NLMG patients, although the incidence of glomerular IgM was somewhat higher in LMG patients. IgA deposition was twice as frequent in LMG as NLMG patients ($P > 0.05$, < 0.1). The difference between LMG and NLMG in the incidence of C1q deposition was significant ($P < 0.01$) but became even more significant ($P < 0.001$) if only intense (> or = 2+) staining was considered. ANA bound to nuclei (Fig. 6) were observed in a minority of LMG patients but never in NLMG patients. In general patients with overt LMG showed a greater deviation from the usual immunohistopathologic features of NLMG than did patients with latent LMG but latent LMG glomeruli did show substantially more C1q staining than NLMG glomeruli.

Statistical analysis. Table 4 gives a compilation of the diagnostic utility of the parameters studied for differentiating

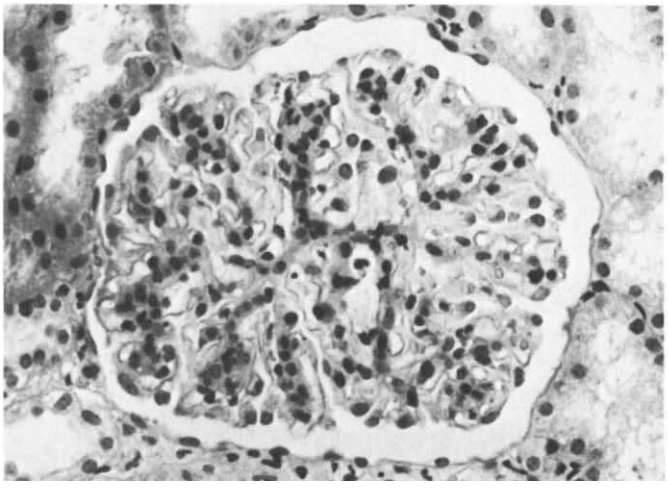

Fig. 3. *Mesangial hypercellularity in a patient with nonlupus membranous glomerulopathy.* Hypercellularity was present in a repeat biopsy 25 months later. No mesangial or subendothelial dense deposits, IgA, or C1q were observed in this patient. (hematoxylin and eosin, ×300)

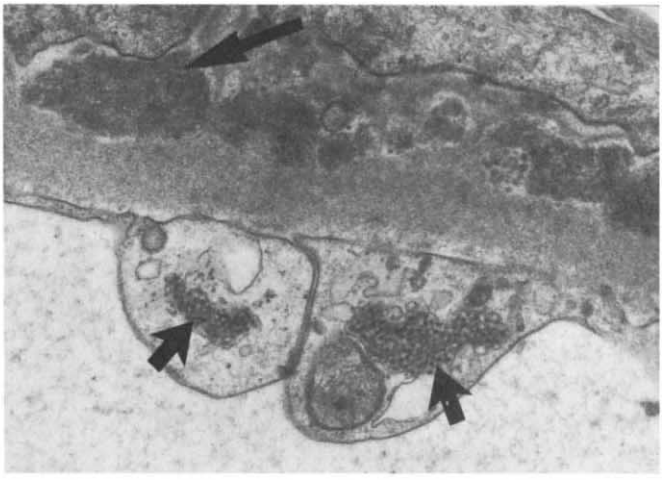

Fig. 4. *Electron micrograph of a glomerular capillary wall showing supepithelial electron dense deposits* (long arrow) *and endothelial tubuloreticular inclusions* (short arrows). (×5,000)

between NLMG and LMG. The values obtained are minimum values since it is possible that within the NLMG group there are patients who will eventually develop SLE, or who have, unknown to us, developed SLE since the time of biopsy. The pathologic features with the highest sensitivity for LMG versus NLMG are serum ANA and mesangial dense deposits. However, patients with latent LMG had serum ANA only 67% of the time when biopsied although they all had ANA when a diagnosis of SLE was eventually made. Six of the features analyzed had 90% or better specificity for LMG. TBM deposits and tissue ANA had 100% specificity and therefore 100% positive predictive value, but their low sensitivity decreased their overall diagnostic efficiency. In general, pathologic features had better negative than positive predictive value, therefore making their absence more useful in ruling out LMG than their presence was in diagnosing LMG. Serum ANA was most efficient in differentiating LMG from NLMG, followed in order by subendothelial dense deposits, mesangial dense deposits, hypocomplementemia, endothelial tubuloreticular inclusions, tubular basement membrane deposits, tissue ANA, and intense C1q deposition. Glomerular deposits of IgA or combined IgG, IgA, and IgM, and glomerular hypercellularity were least efficient at differentiating LMG from NLMG.

The simultaneous occurrence in MG patients of more than one pathologic feature results in a greater specificity and positive predictive value for LMG than would be the case for the isolated occurrence of one of the features (lines *(12)*, *(13)*, and *(14)* in Table 4). However, requiring more than one parameter to be present before making a diagnosis of LMG would reduce the sensitivity and negative predictive value of the parameters.

Discussion

LMG differs from NLMG in clinical, serologic, morphologic, and immunohistopathologic respects. In patients with definite clinical evidence for SLE at the time of biopsy these distinguishing pathologic features of LMG are redundant for establishing a pathogenetic relationship between the MG and SLE.

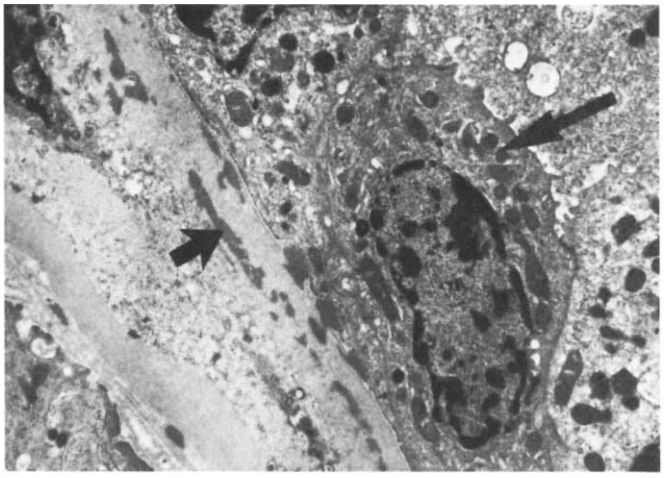

Fig. 5. *Electron micrograph showing tubular epithelial cells* (long arrow) *and electron dense deposits* (short arrow) *within the tubular basement membrane of a patient with lupus membranous glomerulopathy.* (×5,000)

However, on occasion one or more of these features will be observed in a patient with MG and without a clinical diagnosis of SLE. The data presented in this publication were compiled in an attempt to determine the relative accuracy of certain serologic, morphologic, and immunohistopathologic features for differentiating between LMG and NLMG, and to offer some guidance for predicting the likelihood that a patient with MG with these features in fact has LMG rather than NLMG whether or not clinical data are available to support this contention.

At the time SLE was diagnosed, 96% of our LMG patients had four or more American Rheumatism Association lupus criteria. Cohen and Canoso [5] found that 94% of SLE patients fulfill four or more of these criteria. On the average, our LMG patients were slightly younger and much more often female than NLMG patients. A slight male preponderance in NLMG is well documented in the literature [9, 10]. Marked predominance of

Table 3. Immunohistopathologic data from lupus and nonlupus membranous glomerulopathy specimens

Group	Immunohistopathologic feature								
	IgG	IgM	IgA	IgGMA	C3	C4	C1q	≥2 + C1q	Tissue ANA
NLMG	99[a] (121/122)[b]	47 (57/122)	16 (20/122)	13 (16/122)	85 (103/121)	33 (34/103)	23 (18/78)	11 (9/78)	0 (0/101)
LMG	100 (21/21)	62 (13/21)	38 (8/21)	29 (6/21)	95 (20/21)	47 (8/17)	67 (8/12)	67 (8/12)	17 (3/18)
Overt LMG	100 (16/16)	75 (12/16)	44 (7/16)	37 (6/16)	94 (15/16)	43 (6/14)	70 (7/10)	70 (7/10)	20 (3/15)
Latent LMG	100 (5/5)	20 (1/5)	20 (1/5)	0 (0/5)	100 (5/5)	67 (2/3)	50 (1/2)	50 (1/2)	0 (0/3)

Abbreviations: NLMG, nonlupus membranous glomerulopathy; LMG, lupus membranous glomerulopathy.
[a] The value represents percent of patients with a given immunopathologic feature.
[b] The value represents the number of patients positive/number of patients examined.

females with LMG was also reported by Baldwin et al (14 of 14 LMG were female) [2] and Appel et al (9 of 10 LMG were female) [11]. Blacks accounted for 26% of NLMG patients as compared with 87% of LMG. Our referral population (North Carolina) has 22% blacks and our renal biopsy population as a whole has 26% blacks. Appel et al [11] noted 70% of LMG patients were black, although only 41% of all lupus glomerulonephritis patients were black.

Only 2% of NLMG patients had hypocomplementemia compared with 65% of LMG patients. Seventy-five percent of overt LMG patients had hypocomplementemia. The frequency of hypocomplementemia in NLMG patients has been reported to be 3% [10] and 5% [12]. Hypocomplementemia was found in a majority of LMG patients by Donadio, Burgess, and Holley [4] and in 75% by Appel et al [11].

In our study, 7% of NLMG and 100% of LMG patients at the time a diagnosis of SLE was made had ANA. Gaffney and Panner [13] found no ANA in 41 patients with NLMG. ANA were detected in 78% of LMG patients by Donadio, Burgess, and Holley [4] and in 50% by Appel et al [11]. In our patients, serum ANA had a very high negative predictive value, that is, if absent, a diagnosis of SLE was unlikely. However, only 67% of the latent LMG patients had serum ANA at the time MG was first recognized, even though they eventually all demonstrated ANA. Thus, no detectable serum ANA at the time of biopsy does not eliminate eventual development of clinically overt SLE. Although ANA are of low frequency in NLMG patients, the small percentage of these patients with ANA results in a disproportionate reduction in positive predictive value since the NLMG group accounts for 84% of all MG patients. Although less sensitive for LMG than serum ANA, hypocomplementemia was more specific and thus had a higher positive predictive value.

NLMG is usually considered to have no glomerular hypercellularity, albeit quantitative morphometry has revealed mesangial hypercellularity [13, 14]. Some glomerular hypercellularity has been noted in LMG and has been suggested to be of value in differentiating between LMG and NLMG [2, 15]. In our patients, glomerular hypercellularity did occur more often in LMG but was the least efficient parameter for differentiating LMG from NLMG.

Mesangial electron dense deposits are common in LMG but uncommon in NLMG [3]. We identified mesangial deposits in 11% of NLMG patients. In other series of NLMG patients mesangial dense deposits were said to be present in 3% by Gaffney and Panner [13], 8.5% by Shearn, Biana, and Hooper [16], and 39% by Honig et al [17]. This latter study reported an unusually high proportion of NLMG patients with mesangial deposits and stated that these patients had atypical clinical features compared with MG patients without mesangial deposits. We have some reservations about the validity of these data since in our opinion their Figure 5 does not show mesangial deposits but shows instead tangentially cut paramesangial subepithelial deposits. Ninety-six percent of our LMG patients had mesangial electron dense deposits. This agrees with the high frequency of mesangial deposits observed in LMG by other investigators [4, 11]. This high sensitivity for LMG results in the highest negative predictive value for mesangial dense deposits of any morphologic feature. That is, if mesangial dense deposits are absent, SLE is not very likely in a MG patient. But the positive predictive value of mesangial deposits is poor; thus, strongly suggesting a diagnosis of LMG on the basis of these deposits alone is unwarranted.

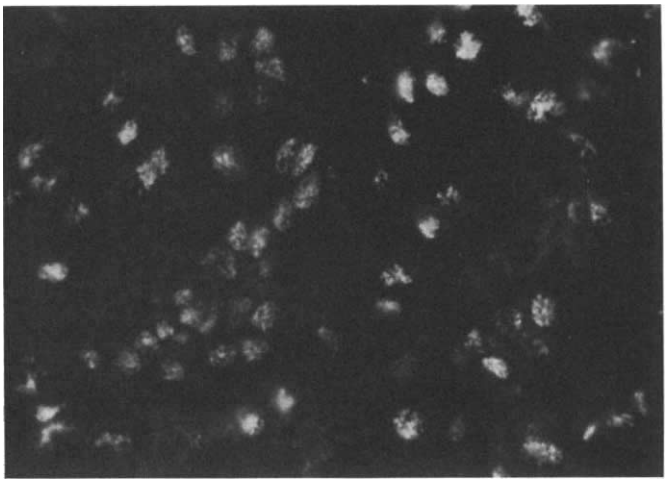

Fig. 6. *Direct immunofluorescence microscopy of renal biopsy tissue from a patient with lupus membranous glomerulopathy showing ANA bound to tubular epithelial nuclei.* (anti-IgG, ×400)

Small subendothelial electron dense deposits were identified in 61% of biopsy specimens included in the LMG group. In most patients these deposits were minute and few in number. Patients with subendothelial deposits had no more glomerular cellularity than patients without them. In one study of LMG, Donadio, Burgess, and Holley [4] excluded SLE glomerulonephritis patients from the MG category if any subendothelial

Table 4. Diagnostic accuracy of pathologic differentiation between lupus and nonlupus membranous glomerulopathy

Parameter	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Efficiency
(1) Serum ANA	100[a]	93	78	100	94
(2) Hypocomplementemia	65	98	89	91	90
(3) Hypercellularity	27	85	26	86	76
(4) Mesangial deposits	96	89	63	99	90
(5) Subendothelial deposits	61	96	77	93	91
(6) Tubuloreticular inclusions	79	90	61	96	88
(7) TBM deposits	32	100	100	87	88
(8) IgA deposits	38	84	29	89	77
(9) IgGMA deposits	29	87	27	88	78
(10) Intense C1q	67	88	47	95	86
(11) Tissue ANA	17	100	100	87	87
(12) (4) and *(6)*[b]	79	96	81	96	94
(13) (4), (5) and *(6)*	50	99	88	91	91
(14) (2), (4), (5) and *(6)*	46	100	100	86	88

[a] Serum ANA were present in 67% of latent lupus patients at the time of biopsy but in 100% when a diagnosis of lupus was made.
[b] These data represent combined parameters.

Table 5. Clinical and pathologic data on six patients with latent lupus membranous glomerulopathy

Age	Sex	SLE criteria[a]	Latent period[b]	ANA[c]	Decreased serum C3[c]	Glomerular hypercellularity	Mesangial dense deposits	Tubuloreticular inclusions	Subendothelial deposits	IgA deposits	C1q deposits
32	F	0/4	4	+	0	0	+	+	0	N[d]	N
50	F	0/5	18	0	+	0	+	+	0	0	N
9	M	1/5	7	+	+	0	+	+	0	0	N
42	M	2/5	23	+	0	0	+	0	+	0	N
44	M	2/4	16	+	0	0	+	+	0	0	0
16	F	1/4	4	0	0	0	0	+	0	+	+

[a] The value represents at the time of biopsy/at the time of SLE diagnosis.
[b] The period consists of time in months between biopsy and SLE diagnosis.
[c] Data was taken at the time of biopsy.
[d] N = not done.

deposits were present, although in another publication Donadio and Holley [18] acknowledged the presence of subendothelial deposits in some patients with LMG. Other investigators have also noted the occurrence of subendothelial electron dense deposits in LMG [11, 19]. In our patients, subendothelial deposits were more frequent in patients with overt (73%) rather than latent (17%) SLE.

The high frequency of tubuloreticular inclusions (TRI) in lupus glomerulonephritis compared with other glomerulopathies is well known [20–26]. TRI were identified in 79% of our LMG patients. During the interval of study reported in this publication we identified TRI in 93% of 61 lupus glomerulonephritis patients not categorized as LMG. Therefore, although frequent in LMG, TRI are more frequent in the proliferative variants of lupus glomerulonephritis. TRI were identified in 10% of our NLMG specimens. The combined data from four reports in the literature indicate 5% (9 of 186) of NLMG patients with TRI [20, 22, 25, 27].

Tubular basement membrane (TBM) deposits are common in lupus glomerulonephritis but rarely found in NLMG [3]. We identified TBM deposits in 32% of LMG biopsy specimens but 0% of NLMG biopsy specimens. Lehman, Wilson, and Dixon [28] found 56% (18 of 32) of lupus glomerulonephritis patients to have granular TBM deposits by immunofluorescence microscopy, but none of 26 MG specimens had TBM deposits. Brentjens et al [29] noted by immunofluorescence microscopy TBM deposits in 53% of lupus glomerulonephritis patients. However, while 66% of diffuse proliferative lupus glomerulonephritis patients had TBM deposits, only 40% of LMG patients had deposits. They saw one of 34 NLMG biopsy specimens demonstrating TBM deposits by immunofluorescence microscopy, but this was not confirmed by electron microscopy. TBM deposits are therefore very specific for LMG and have a high positive predictive value, but they are insensitive and therefore have an overall diagnostic efficiency of less than 90%.

By immunofluorescence microscopy there was no statistically significant ($P > 0.1$) difference between LMG and NLMG in the frequency of IgG, IgM, C3, or C4 glomerular deposition. IgA and C1q occurred at a significantly higher frequency in LMG, but the frequency of intense (2+ or more) C1q deposition was most significantly ($P < 0.001$) elevated in LMG compared with NLMG. Such high intensity C1q staining has been reported previously in lupus glomerulonephritis and may result from binding of C1q to DNA as well as to Ig [30].

Immunoglobulins, presumably ANA, bound to nuclei in the biopsy specimen were noted in 17% of LMG patients (only in overt SLE patients) compared with 0% of NLMG biopsy specimens. The nuclear staining usually had a speckled pattern.

McCoy [31] observed tissue ANA in 32% (6 of 19) of SLE glomerulonephritis biopsy specimens, including three LMG patients but saw no tissue ANA in any of 225 renal biopsy specimens from patients who did not have SLE. Therefore, tissue ANA has 100% specificity and positive predictive value for LMG but very low sensitivity.

In one series of 150 SLE patients, 6% presented with renal disease, usually nephrotic syndrome, as the initial manifestation [32]. Reported in the literature are 12 patients with MG and no clinical evidence for SLE who subsequently developed overt SLE after 5 months to 7 years [22, 33–37]. Many of these patients were noted to have endothelial TRI in the initial biopsy tissue sample. Six of our LMG patients did not exhibit clinical evidence for SLE at the time of biopsy, but were later found to have SLE after an average interval of 1 year (Table 5). These patients with latent SLE had a lower incidence of hypocomplementemia and serum ANA than overt SLE patients, and the frequency in them of the morphologic and immunohistopathologic parameters analyzed tended to be intermediate relative to NLMG and overt LMG, but usually more closely approximated the overt LMG values. All patients with latent LMG had at least two of the following features: TRI, mesangial dense deposits, small subendothelial dense deposits, or intense C1q. Therefore, although clinical evidence for SLE was lacking at the time of biopsy, there was pathologic evidence suggesting LMG rather than NLMG in all six patients with latent LMG.

In general, the serologic, morphologic, and immunohistopathologic features analyzed were better at ruling out SLE than making a diagnosis of LMG. This is indicated by six parameters having negative predictive values greater than 90% as compared with only two parameters (both of very low sensitivity) having positive predictive values greater than 90%. However, the significantly different incidence in LMG versus NLMG of a number of these features warrants suggesting the possibility of unrecognized or nascent SLE in certain patients found to have MG displaying these features. In addition, the specificity and positive predictive value of pathologic features increases when, as is often the case, more than one is observed in a given biopsy specimen. However, since requiring the presence of multiple parameters before making a diagnosis of LMG would reduce the sensitivity and negative predictive values of the parameters, the overall diagnostic efficiency for discriminating between LMG and NLMG would not be altered significantly. But, for individual cases, the simultaneous occurrence of multiple pathologic features with some degree of specificity for LMG substantially enhances the positive predictive values for LMG. Therefore, from our data, although individually, mesangial dense deposits, subendothelial dense deposits, and tubuloreticular inclusions have positive predictive values of 61 to 77, the simultaneous occurrence of these three parameters results in a positive predictive value of 88 and increases to 100 if hypocomplementemnia is also present.

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