Clin Exp Nephrol (2015) 19:395–402
DOI 10.1007/s10157-014-1002-1

ORIGINAL ARTICLE

Lupus-like membranous nephropathy: Is it lupus or not?

Ramin Sam · Amit Joshi · Sam James · Kuang-Yu Jen · Firouz Amani · Peter Hart · Melvin M. Schwartz

Received: 24 October 2013 / Accepted: 12 June 2014 / Published online: 4 July 2014

Abstract
Background Membranous glomerulonephritis is typically classified as idiopathic or secondary to systemic lupus erythematosus (SLE), hepatitis B, drugs, toxins, other infections, or malignancy. Not infrequently in some patients without a definite diagnosis of SLE, pathologic features of secondary membranous nephropathy are seen e.g., mesangial and/or subendothelial deposits, tubuloreticular inclusions, and full house immunofluorescence. In these patients, there is uncertainty about the etiology, response to therapy, and prognosis of membranous GN.
Methods We retrospectively reviewed the charts of 98 patients with membranous GN at San Francisco General Hospital and John Stroger Hospital of Cook County over a 10-year period. Data were collected and analyzed using SPSS.18.
Results Thirty-nine (40 %) had idiopathic membranous GN (Group 1), thirty-six (37 %) had lupus membranous GN (Group 2) and twenty-three (23 %) had some pathological features of secondary membranous GN, but no definite etiology of membranous GN (Group 3). At baseline (at time of renal biopsy) and after mean follow-up of 3.5 years, the average serum creatinine (in mg/dL) in Group 1 was (1.6 ± 1.0 versus 1.6 ± 1.7), Group 2 was (1.8 ± 2.5 versus 1.2 ± 0.9) and Group 3 was (1.1 ± 0.4 versus 1.27 ± 0.83), respectively. For the same time points, the average urine protein to creatinine ratio (g/g) in Group 1 was (9.8 ± 7.1 versus 5.7 ± 6.7), Group 2 was (4.2 ± 3.9 versus 1.7 ± 2.2), and Group 3 was (7.4 ± 5.7 versus 3.1 ± 3.8). In addition, during the follow-up period, eleven of 39 (28 %) in Group 1, two of 36 (6 %) in Group 2, and three of 23 (13 %) in Group 3 progressed to end-stage renal disease and were started on dialysis.
Conclusions It appears that patients with lupus membranous GN have better renal prognosis than patients with idiopathic membranous GN. The renal prognosis for patients with pathological features of lupus membranous but no diagnosis of systemic lupus (lupus-like membranous GN) falls in between. Further studies are needed to determine if Group 3 patients can (a) definitively be classified as true idiopathic membranous GN or lupus membranous GN or (b) they have a separate disease from either M-type phospholipase A_2 receptor membranous nephropathy or systemic lupus-induced membranous nephropathy.

Keywords Membranous GN · Systemic lupus · Idiopathic membranous · Pathological features of lupus membranous

R. Sam (✉) · S. James
Division of Nephrology, San Francisco General Hospital and the University of California, 1001 Potrero Ave, Building 100, Rm 342, San Francisco, CA 94110-1341, USA
e-mail: Samr@medsfgh.ucsf.edu

A. Joshi · P. Hart
Division of Nephrology, Stroger Hospital of Cook County, Chicago, IL, USA

K.-Y. Jen
Department of Pathology, University of California, San Francisco, CA, USA

F. Amani
Department of Biostatistics, Ardabil University of Medical Sciences, Ardabil, Iran

M. M. Schwartz
Department of Pathology, Rush Medical College, Chicago, IL, USA

Introduction

More than 50 years ago, it was recognized that there are a group of patients with membranous GN who have pathological features of lupus nephritis, but not a diagnosis of systemic lupus erythematosus (SLE). In 1964, Simenhoff and Merrill stated that "lupus nephritis may present as a renal syndrome only, without any of the other manifestations of SLE [1]." The problem with labeling these patients as renal-limited lupus is that systemic lupus suggests a 'systemic disease' that is not limited to one organ. It is likely that the pathogenesis of membranous nephropathy is autoimmune, thus stating that these patients have renal-limited lupus adds little to current understanding and natural history of this disease. It is true that some of the patients labeled as "latent lupus" and not SLE at the time of kidney biopsy subsequently were diagnosed with SLE years later. However, the criteria for diagnosing SLE have changed over the years (many of the patients with latent lupus were diagnosed using the LE cell preps which are no longer used), and it is not documented what percentage of patients with pathological features of membranous lupus nephritis but no diagnosis of SLE subsequently developed SLE. At the time of kidney biopsy, it is important to determine if membranous GN is primary or secondary in nature, because pathogenesis, treatment response and prognosis differ in each disease group. We evaluated 98 patients with membranous nephropathy and attempted to determine renal prognosis depending on whether they have idiopathic, lupus or 'lupus-like' membranous GN.

Methods

All kidney biopsy reports at San Francisco General Hospital between 1998 and 2008 and at John Stroger Hospital of Cook County in Chicago between 2001 and 2008 were reviewed. All patients with histologic diagnosis of membranous GN were selected. Only patients with membranous lupus nephritis (class V by the ISN/RPS 2003 classification) were included for analysis; those with class V and concurrent class III or class IV lupus nephritis were excluded. Subsequently, the electronic medical records of 31 patients with membranous GN at San Francisco General Hospital and 67 patients at John Stroger Hospital of Cook County were reviewed. The patients were then divided into 3 groups. Group 1: idiopathic membranous GN with no pathological features of secondary membranous GN, Group 2: membranous lupus nephritis by both clinical and pathologic criteria, Group 3: "lupus-like" membranous GN in which pathological features of membranous lupus nephritis are present without a clinical diagnosis of SLE. The pathological features of membranous lupus nephritis included a combination of mesangial deposits, subendothelial deposits, mesangial hypercellularity, tubuloreticular inclusions, intense C1q staining on immunofluorescence microscopy and/or full house immunofluorescence pattern, and tubular basement membrane deposits (Fig. 1). The pathological features were enough to make the pathologist comment on the report that systemic lupus should be ruled out. IgG subclass staining was performed for IgG1, IgG2, IgG3, and IgG4 using primary antibody (Invitrogen) dilutions at 1:120, 1:120, 1:60, and 1:120, respectively. Secondary FITC-labeled goat anti-mouse IgG antibody (Invitrogen) was used at 1:80 dilution for antigen detection.

Baseline medical history and laboratory results, treatment administered and long-term follow-up laboratory results were collected on all patients. Collected data were analyzed using SPSS.18 software. For quantity variables, we used ANOVA to determine statistically significance differences (p value <0.05) between means of the groups for both baseline and follow-up characteristics. To compare means in two groups, we used Post Hoc Tukey method. Also to compare between two quality variables, we used the Chi-Square test.

This study was approved by the local ethics committee (institutional review board) and need for informed consent was waived (#13- 11936).

Results

Of the 98 patients, 39 (40 %) had idiopathic membranous GN, 36 (37 %) had membranous lupus nephritis, and 23 (23 %) had "lupus-like" membranous GN (Table 1). The incidence of idiopathic membranous GN, membranous lupus nephritis, and "lupus-like" membranous GN was 36, 36, and 29 % at South Francisco General Hospital and 42, 37, and 21 % at Stroger Hospital, respectively.

The baseline characteristics of patients with idiopathic membranous GN, membranous lupus nephritis, and "lupus-like" membranous GN are summarized in Table 2. Patients with idiopathic membranous GN were significantly older than patients with membranous lupus nephritis or "lupus-like" membranous GN (46 versus 37 versus 38 years, respectively). Gender ratio was >2:1 favoring men with idiopathic membranous GN, and reversed to almost 2:1 favoring women with membranous lupus nephritis, and equal in patients with "lupus-like" membranous GN. There were more Asians and less Hispanics and Whites with membranous lupus nephritis compared to idiopathic membranous GN. The baseline Creatinines for Groups 1, 2, 3 were 1.6, 1.8, and 1.1 mg/dL, respectively. Patients with idiopathic membranous GN had more baseline proteinuria (9.8 g/d) compared to patients with lupus membranous GN (4.2 g/d) and "lupus-like" membranous

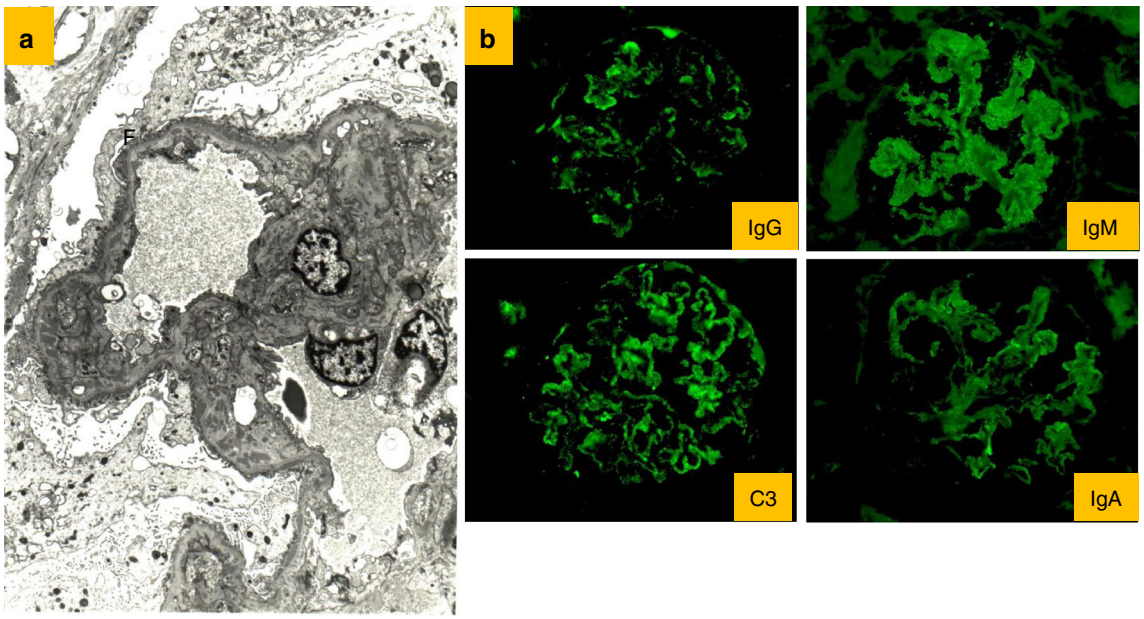

Fig. 1 Representative pictures of two patients with lupus-like membranous nephropathy. In **a** electron micrograph is shown with lots of mesangial deposits. **b** shows immunofluorescence of another patient with positivity for IgG, IgM, C3, and IgA

Table 1 Incidence of primary versus secondary membranous nephropathy

Type of membranous GN	SFGH # of cases (% of total)	CCH # of cases (% of total)	Total # of cases (% of total)
Idiopathic membranous (Group 1)	11 (35.5 %)	28 (41.8 %)	39 (39.8 %)
Lupus membranous (Group 2)	11 (35.5 %)	25 (37.3 %)	36 (36.7 %)
Lupus-like membranous (Group 3)	9 (29.0 %)	14 (20.9 %)	23 (23.5 %)

SFGH San Francisco General Hospital, *CCH* Cook County Hospital

GN (7.4 g/d). All the patients in the membranous lupus nephritis group tested positive for ANA at least on one occasion, whereas ANA positivity was 27 % in the idiopathic membranous GN group and 52 % in the "lupus-like" membranous GN group. Only three patients out of the entire cohort tested positive for hepatitis B (3 %). By comparison, 7 out of 101 (6.9 %) of our current dialysis patients were positive for hepatitis B. Because the incidence of hepatitis B was the same in patients with membranous nephropathy and our dialysis patients (who did not have membranous nephropathy), we do not believe hepatitis B was causative of the membranous nephropathy in these patients. Hepatitis C was seen frequently in our patients, consistent with the high incidence of hepatitis C in the two County hospitals. Again, 13 out of the 98 (13 %) patients with membranous nephropathy had hepatitis C, this compares with 24 out of 101 (23.8 %) of our dialysis patients who were positive for hepatitis C. The corresponding numbers for HIV positivity were 4/98 (4 %) for membranous nephropathy and 6/96 (6.3 %) for dialysis patients. The average serum albumin and serum cholesterol concentrations were 2.5, 2.4, 2.5 g/dL, and 317, 226, and 272 mg/dL in idiopathic membranous GN, membranous lupus nephritis, and "lupus-like" membranous GN groups, respectively. To summarize, patients with idiopathic membranous had more proteinuria and higher cholesterol levels at baseline compared to patients with membranous lupus nephritis.

The follow-up data are summarized in Table 3. In general, patients with idiopathic membranous GN were treated more often with ACEI, ARB, cyclosporine, and cyclophosphamide, whereas patients with membranous lupus nephritis received more prednisone, mycophenolate, and azathioprine. The lupus-like patients also received ACEI, ARB, and prednisone with some patients receiving additional agents. The average serum creatinine after an average of 3.5 years of follow-up was 1.6, 1.2, and 1.3 mg/dL in idiopathic membranous GN, membranous lupus nephritis, and "lupus-like" membranous GN groups, respectively. The average proteinuria after 3.5 years of follow-up was 5.7, 1.7, and 3.1 g/d, respectively, showing statistically significant difference between the idiopathic

Table 2 Summary of baseline characteristics of the 3 groups of patients

Characteristic	Group 1 Idiopathic membranous	Group 2 Lupus membranous	Group 3 Lupus-Like membranous	*p* value
Age	45.9 ± 10.3	37.0 ± 11.7	38.2 ± 11.4	0.001
Sex	28 M, 11 F	13 M, 22 F	10 M, 12 F	0.008
Race	19 AA, 14 H, 4 W, 2 Asian	18 AA, 9H, 8 Asian, 0 W	9 AA, 10 H, 2 Asian, 2 W	0.35
Cr (mg/dL)	1.57 ± 1.04	1.79 ± 2.52	1.07 ± 0.40	0.26
Prot./cr (g/g)	9.8 ± 7.1	4.2 ± 3.9	7.4 ± 5.7	0.001
ANA	9+, 25−	34+, 1−	7+, 12−	0.001
DsDNA	0+, 7−	19+, 15−	2+, 8−	0.006
Anti-Smith	1+, 2−	17+, 15−	1+, 5−	0.286
SSA	1+, 1−	15+, 16−	1+, 4−	0.67
SSB	0+, 2−	4+, 28−	1+, 4−	0.78
RNP	2+, 1−	26+, 5−	4+, 2−	0.62
Hep B/Hep C/HIV	2 Hep B, 7 Hep C, 2 HIV	1 Hep B, 3 Hep C, 1 HIV	0 Hep B, 3 Hep C, 1 HIV	0.92
Alb (g/dL)	2.5 ± 0.6	2.4 ± 1.1	2.5 ± 1	0.97
Chol (mg/dL)	316.6 ± 14.9	226.3 ± 81.8	271.7 ± 174.7	0.019

M male, *F* female, *AA* African American, *W* white, *H* hispanic, *Cr* creatinine, *Prot./Cr* urine protein/creatinine ratio

Table 3 Summary of follow-up data on the 3 groups of patients

Follow-up data	Group 1 Idiopathic membranous	Group 2 Lupus membranous	Group 3 Lupus-like membranous	*p* value
Last Creatinine (mg/dL)	1.63 ± 1.66	1.17 ± 0.94	1.27 ± 0.83	0.35
Years after biopsy	3.0 ± 2.5	4.2 ± 2.7	3.5 ± 2.8	
Last Albumin(g/dL)	3.45 ± 0.91	3.61 ± 0.80	3.52 ± 0.83	0.82
Years after biopsy	3.5 ± 2.7	4.6 ± 3.1	3.4 ± 3.3	
Last Prot./cr (g/g)	5.73 ± 6.73	1.69 ± 2.20	3.13 ± 3.83	0.004
Years after biopsy	3.2 ± 2.5	3.8 ± 2.5	2.9 ± 1.9	
Treatment data	13Pred, 26ACE, 11ARB, 10cyclos, 8cytoxan, 2MMF, 1Aza	33Pred, 15ACE, 5ARB, 2 cyclos, 6cytoxan, 13MMF, 8Aza	6Pred, 14ACE, 4ARB, 2cyclos, 2cytoxan, 2MMF, 1Aza	

Dialysis patients were assumed to have a serum creatinine of 8.0 mg/dL

Pred prednisone, *ACE* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *MMF* mycophenolate, *Aza* azathioprine, *Prot./cr.* urine protein/creatinine ratio

membranous GN and the other 2 groups. The average serum albumin after 3.5 years of follow-up was 3.5, 3.6, and 3.5 g/dL, respectively. Thus, it seems that after an average follow-up of 3–4 years, the average proteinuria and serum creatinine were lower in patients with membranous lupus nephritis than in those with idiopathic membranous GN, and the patients with "lupus-like" membranous GN fell in between these values.

Five of the patients with "lupus-like" membranous GN had IgG subclass staining, of which four had strongest staining with IgG4 and one patient had IgG1 (Table 4). The staining pattern was mainly around capillary loops, although some mesangial staining was also present. None of the patients in the lupus-like group went on to have a definite diagnosis of systemic lupus; however, a few of these patients who were ANA negative at the beginning went on to develop ANA positivity. Eleven of 39 (28 %) patients in the idiopathic membranous GN group, two of 36 (6 %) patients in the lupus membranous GN group, and three of 23 (13 %) patients in the lupus-like membranous GN group progressed to ESRD and were started on chronic

Table 4 IgG subclass staining in 5 patients with lupus-like membranous nephropathy

Patient #	IgG1	IgG2	IgG3	IgG4
6	0	0	0	1+
23	2+	Tr+	Tr+	1+
1	Tr+	2+	0	3+
20	0	Tr+	Tr+	3+
13	0	1+	0	3+

dialysis during the follow-up period. The 3 patients (7.6 %) who died were in the idiopathic membranous GN group.

Discussion

At times in patients with nephrotic syndrome due to membranous GN, histologic findings of membranous lupus nephritis are present without the clinical diagnosis of systemic lupus erythematosus (SLE). In 1976, Libit et al. described three such pediatric patients who subsequently developed SLE after an average follow-up of 2.2 years [2] and the term latent lupus has been used to describe these patients. To our knowledge, there have only been 21 patients described in the literature with latent lupus (10 female, 5 male, and six unknown gender). Their average age was 24.7 years and follow-up was 2.3 years (data were available in 16 patients). Additional data were available in seven of the patients, three had complete remission, two had partial remission, one died, and one developed renal failure [1–8]. In 1983, Jennette et al. [9] established the pathological findings most often seen in membranous lupus nephritis by examining kidney biopsies of 170 patients with membranous GN (including both patients with established diagnosis of SLE and those with idiopathic membranous GN). Many of the patients with features of membranous lupus nephritis did not have systemic features at the time of kidney biopsy. It is not clear what proportion of these patients progressed to full-blown SLE, although some of them did develop SLE later. Review of the literature indicates that of 77–95 such patients, 21 (25 %) developed SLE after a mean follow-up period of 5 years (Table 5) [7–11]. In addition, the diagnostic criteria for SLE have changed since the publication of many of these papers. In fact, many of the patients previously described in the literature with latent lupus were subsequently diagnosed with systemic lupus using the LE cell preps, which is no longer a common practice.

The percentage of all the cases of membranous GN caused by membranous lupus nephritis varies between the different studies, although the average of these studies is 24 % while 62 % were idiopathic membranous GN [9, 12–19]. There were 1368 patients with membranous GN in all of these studies. Other secondary causes accounted for another 14 % of membranous GN cases. Interestingly, in one Chinese study of 390 patients with membranous nephropathy, 12.1 % of the patients had hepatitis B, which is close to the 11 % incidence of hepatitis B in the general Chinese population [13, 20]. In the same study, the incidence of malignancy-associated membranous nephropathy was 3.1 %, which is somewhat lower than the 8.4 % incidence found by Burstein et al. in 1993 [13, 21]. Thus, even though hepatitis B and malignancy are likely implicated in membranous GN, it should be emphasized that they are uncommon causes (more often association rather than true causation), whereas SLE is a common cause of membranous GN.

In recent years, IgG subclass staining has been used to classify the different types of membranous GN. With idiopathic membranous GN, IgG4 clearly predominates. On the other hand, with membranous lupus nephritis and malignancy-associated membranous GN, although a large amount of IgG4 staining is present, significant IgG3 staining is detected with membranous lupus nephritis and IgG1 and IgG2 staining is often seen in malignancy-associated membranous GN [18, 22, 23]. When the kidney biopsy of five of our patients with "lupus-like" membranous GN was stained for IgG subclass, four had strong IgG4 staining, while one had strong IgG1 staining. Thus, the IgG subclass staining in most of these patients was consistent with idiopathic membranous GN.

The classification of membranous GN into idiopathic and secondary causes is only important if there is a difference in the prognosis or response to therapy in the two groups. There are few studies on this topic and none comparing the two groups in the same population of patients. To get some perspective on this, we summarized the treatment data for idiopathic membranous GN and membranous lupus nephritis from a number of studies (Table 6). We found that in patients with idiopathic membranous GN, 21 % of patients that were not treated had partial or complete remission of proteinuria, 81 % of patients treated with cyclosporine had partial or complete remission, and 61 % of patients treated with cytotoxic

Table 5 Prevalence of latent lupus among patients with membranous nephropathy and pathology suggesting systemic lupus

Study	# of patients	# developing lupus	% developing lupus	Follow-up period	Pathologic abnormality
Jennette [9]	16–34	6	18–37 %	1 year	Mixture
Adu [7]	10	4	40 %	14 years	Mixture
Gianviti [10]	4	1	25 %	5.8 years	Full house
Yang [11]	36	9	25 %	NA	TRI
Wen [8]	11	1	9 %	2 years	Full house
Summary	77–95	21	22–27 %	5 years	

NA not available, *TRI* tubuloreticular inclusions

agent plus prednisone had partial or complete remission [24–29]. The studies on membranous lupus nephritis used different immunosuppressive agents and the response rate for proteinuria remission was 66 % [30–33]. The incidence of renal failure in patients with idiopathic membranous GN was 13 % when treated with cyclosporine and 16 % when treated with combination cytotoxic agent and prednisone. In patients with membranous lupus nephritis, the incidence of renal failure was 10 %. However, this data have limitations due to different time periods, different geographic locations with different patient populations, and different duration of follow-up, etc.

To compare the prognosis of idiopathic membranous GN, membranous lupus nephritis, and "lupus-like" membranous GN, we evaluated all the patients with membranous GN in the two county hospitals over a 10-year period. At baseline, patients with idiopathic membranous GN were older and more often men compared to patients with membranous lupus nephritis. They also had more proteinuria and higher serum cholesterols than patients with membranous lupus nephritis. Patients with "lupus-like" membranous GN had baseline characteristics somewhere in between the other two groups. At the end of follow-up, 28 % of patients in the idiopathic membranous GN group, 6 % in the membranous lupus nephritis group, and 17 % in the "lupus-like" membranous GN group were on dialysis. The serum creatinine and proteinuria were also higher in patients with idiopathic membranous GN versus

Table 6 Summary of some studies on prognosis and response to treatment of idiopathic membranous and lupus membranous nephropathy

Author Idiopathic/ Lupus	Year	Drug used	# of patients	% having remission	% with renal failure	Follow-up
Ponticelli [24]	1989	Prednisone	81	Control (23 %)	Control (49 %)	2–11 years
Idiopathic		chlorambucil		Treated (67 %)	Treated (10 %)	
Guasch [25]	1992	Cyclosporine	14	71 %	29 %	12 weeks
Idiopathic						
Cattran [26]	2001	Cyclosporine	51	Control (22 %)	Control (9 %)	78 weeks
Idiopathic		Prednisone		Treated (75 %)	Treated (7 %)	
Yao [27]	2001	Cyclosporine	30	Control (13 %)	0 %	15 months
Idiopathic				Treated (80 %)		
Alexopoulos [28]	2006	Cyclosporine	51	84 %	0 %	12 months
Idiopathic		Prednisone				
Goumenos [29]	2007	Prednisone	77	Cyclosporin (85 %)	Cyclosp (26 %)	
Idiopathic		Cyclosporine			Cytotoxic (23 %)	
		Cytoxan		Cytotoxic (55 %)		
Summary		Prednisone	304	Control (21 %)	Control (34 %)	3.0 years
Idiopathic		Cyclosporine		Cyclosp. (81 %)	Cyclosp. (13 %)	
		Cytoxan/ Chlorambucil		Cyt./chlor. (61 %)	Cyt./chlor. (16 %)	
Donadio [30]	1977	Steroids	28	Control (40 %)	3.6 %	0.16–10 years
Lupus				Treated (17 %)		
Sloan [31]	1996	Steroids	51	37 %	14 %	5.8 years
Lupus		Cytoxan				
		Azathioprine				
Sun [32]	2008	Steroids	100	87 %	7.3 %	77.6 months
Lupus		Chinese herb				
		Cyclosporine				
		MMF, Cytoxan				
Mok [33]	2009	Steroids	38	89 %	16 %	12 years
Lupus		Azathioprine				
Summary		Steroids	217	Treated (66 %)	10 %	7.8 years
Lupus		Other Immunosupp.				

patients with membranous lupus nephritis. Again, patients with "lupus-like" membranous GN had values between the other two groups. Thus, from this data, it seems membranous lupus nephritis is a more benign kidney disease and/or more responsive to treatment than idiopathic membranous GN. Patients without a diagnosis of SLE at the time of biopsy, but have one or more features of membranous lupus nephritis on kidney biopsy, have an intermediate prognosis. The question is whether some of these patients have membranous lupus nephritis and others have idiopathic membranous GN or did they have an undiagnosed disease that is separate from membranous lupus nephritis and idiopathic membranous GN. Since only 25 % of patients with "lupus-like" membranous GN described in the literature eventually developed SLE, it is unlikely that the etiology of the membranous GN in most of these patients is due to either idiopathic membranous GN or membranous lupus nephritis. However, a number of these patients would be reclassified if they were tested for the M-type phospholipase A_2 receptor antibody.

In 2009, a seminal paper was published describing M-type phospholipase A_2 receptor as the target antigen in idiopathic membranous GN [34]. The authors found that 70 % of patients with idiopathic membranous GN had antibodies to this antigen as the likely causative agent for membranous GN. The discovery of the culprit antigen in most cases of idiopathic membranous GN (if and when it is available for widespread use) may make it necessary to redefine our nomenclature for membranous GN. The subgroup of idiopathic membranous GN patients who have antibodies to M-type phospholipase A_2 receptor should be classified as a distinct entity. The patients with a clear cause for secondary membranous GN should be classified as such. Future research may reserve the term idiopathic membranous GN only for patients who are M-type phospholipase A_2 receptor antibody negative and have no clear cause for secondary membranous GN. This new classification may help in the design of future research in patients with membranous GN.

Conflict of interest There are no conflicts of interests in this manuscript.

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