Membranous Nephropathy in Systemic Lupus Erythematosus: Long-Term Outcome and Prognostic Factors of 103 Patients

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Objectives: The objective of this study was to evaluate the clinical features, course, outcome, and prognostic indicators in lupus membranous nephritis (LMN) and to compare data of "pure" LMN vs "mixed" forms.

Methods: We retrospectively examined medical records and kidney biopsies of 103 patients with a diagnosis of LMN.

Results: Sixty-seven patients had "pure" LMN and 36 had "mixed" forms. Patients with mixed LMN had more frequent nephrotic syndrome (66.6 vs 44.7%, $P = 0.05$), low C3 (83.3 vs 62.6%, $P = 0.05$) and C4 (80.5 vs 52.2%, $P = 0.005$), anti-DNA positivity (86.0 vs 62.6%, $P = 0.03$), and a tendency toward a lower creatinine clearance (93 ± 29 vs 112 ± 50 mL/min, $P = 0.07$). Moreover, mixed membranous nephritis had a higher activity and chronicity index (6.5 ± 2.1 vs 1.4 ± 2.03, $P = 0.005$ and 2.4 ± 1.7 vs 1.4 ± 1.8, $P = 0.0001$, respectively). Methylprednisolone pulses and immunosuppressive therapy were more often used in patients with mixed forms (86.1 vs 60.6%, $P = 0.016$ and 83.3 vs 57.5%, $P = 0.008$, respectively). After a mean follow-up of 156.5 ± 104.5 months, there was no difference in the 2 subgroups concerning the number of patients achieving remission and patient/renal survival (94.5 vs 94.0% and 85.8 vs 86% at 10 years). At multivariate analysis, serum creatinine at presentation ($P = 0.0013$), chronicity index ($P = 0.007$), failure of achieving remission ($P = 0.000001$), and occurrence of nephritic flares ($P = 0.00167$) were independent predictors of chronic renal insufficiency.

Conclusions: Despite the differences in clinical and histological presentation, a therapy tailored on the grounds of clinical and histological features may reduce the differences in the outcome of white patients with mixed and pure membranous nephritis.

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Among the different histological classes of lupus nephritis, membranous nephropathy (LMN) accounts for 8 to 20% of all renal biopsies in systemic lupus erythematosus (SLE) patients (1-4). Proteinuria, frequently in the nephrotic range, is almost invariably the clinical presentation of this form, whereas the presence of a mild renal dysfunction is infrequent. It is generally accepted that the prognosis of LMN in SLE seems to be far better than that described for the diffuse proliferative forms, even if in 1 series, LMN

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Table 1 Clinical and Histological Characteristics at Presentation of Patients with Membranous Lupus Nephritis

	All Patients	Pure MN	Mixed MN	*P*
	103	67	36	
Age (yr) mean ± SD	31.3 ± 13.5	30.2 ± 12.9	33.1 ± 14.6	Ns
Duration SLE, mo	54.6 ± 64	52.6 ± 62.8	63.6 ± 66.5	Ns
Duration LN, mo	20.9 ± 37.9	23.29 ± 37.01	16.58 ± 39.58	Ns
Sex F/M, no. patients	92/11	57/10	35/1	Ns
Serum creatinine, mg/dL	0.87 ± 0.4	0.9 ± 0.45	0.83 ± 0.28	Ns
Creatinine clearance, mL/min	105.1 ± 43.9	112 ± 50	93 ± 29	0.07
Renal insufficiency, no. patients (%)	13 (12.6%)	11 (16.4%)	2 (5.5%)	Ns
Proteinuria g/24 h	4.2 ± 2.9	3.96 ± 3.16	4.69 ± 2.58	0.06
Nephrotic syndrome, no. patients	54 (52.4%)	30 (44.7%)	24 (66.6%)	0.05
Arterial hypertension, no. patients	35 (33.9%)	23 (34.3%)	12 (33.3%)	Ns
Hematocrit, %	36.5 ± 5	36.6 ± 5.3	31.9 ± 4.3	Ns
White blood cells/mmc	6040 ± 2466	5654 ± 2041	6029 ± 3321	Ns
Platelets	239,802 ± 102,635	228,000 ± 101,891	249,000 ± 104,483	Ns
Low C3, no. patients	72 (69.9%)	42 (62.6%)	30 (83.3%)	0.05
Low C4, no. patients	64 (62.1%)	35 (52.2%)	29 (80.5%)	0.005
Anti-DNA positivity	73 (70.8%)	42 (62.6%)	31 (86%)	0.03
Activity index	3 ± 3	1.4 ± 2.03	6.5 ± 2.1	0.005
Chronicity index	2 ± 2	1.4 ± 1.8	2.4 ± 1.7	0.0001
SLEDAI score	13.9 ± 2.33	12.9 ± 5.1	15.8 ± 4.88	0.008
aPL positivity, no. patients pos/neg	23/85	17/55	6/30	Ns
Mean follow-up mo	156 ± 105	176.7 ± 106.3	121.7 ± 92.9	0.01
MMP/oral prednisone/none	68/31/4	37/26/4	31/5	0.016
Total IS therapy	65 (63%)	35 (57.5%)	30 (83.8%)	0.008
Cyclophosphamide or chlorambucil[a]	50 (48.5%)	25 (41%)	25 (69.4%)	0.004
Other IS therapy	15 (14.5%)	10 (15%)	5 (13.8%)	Ns
Maintenance immunosuppressive therapy	46 (44.6%)	21 (34%)	25 (81%)	0.0014
ACE inhibitors/ARB	80 (77.6%)	51 (75%)	29 (80.6%)	Ns
Aspirin	34 (33%)	18 (31%)	16 (50%)	Ns

SLE, systemic lupus erythematosus; LN, lupus nephritis; F, female; M, male; aPL, antiphospholipid antibodies; pos, positive; neg, negative; MMP, methylprednisolone pulses; IS therapy, immunosuppressive therapy. Other IS therapy in pure MN: azathioprine 5 patients mycophenolate mofetil 2 patients, cyclosporine 2 patients, metotrexate 1 patient, in mixed MN azathioprine 5 patients. Maintenance immunosuppressive therapy: in pure MN: azathioprine 14 patients, mycophenolate mofetil 2 patients, cyclosporine 5 patients, in mixed MN azathioprine 13 patients, mycophenolate mofetil 8 patients, cyclosporine 4 patients.

P value refers to comparison between pure and mixed LMN.

[a]Cyclophosphamide 40 patients (15 in pure LMN, 25 in mixed LMN), Chlorambucil 10 patients (8 in pure LMN, 2 in mixed LMN).

had the worst prognosis of all the histological classes of lupus nephritis (1).

Few studies have reported the long-term outcome of LMN and with contrasting results. The 10-year patient survival ranges from 55 to 100% and that of renal survival ranges from 47 to 90% (3,5-13). These wide ranges may be attributed to a number of factors. In general, the long-term outcome was worse in studies including both pure LMN and mixed (membranous plus proliferative) forms. As a matter of fact, the majority (3,9,10,14,15), although not all studies (5), show that patients with mixed LMN have a worse 10-year patient and renal survival than that of patients with pure LMN. Few prognostic factors for patient and renal survival have been identified in patients with LMN (4,7,10), probably due to the low number of patients evaluated and/or for the short follow-up of the cohorts.

The aim of the present study is (1) to compare the clinical presentation, the course, and the long-term outcome of patients with pure LMN with those of mixed LMN of a large cohort of SLE patients followed for 13 years in 2 Italian renal units; (2) to identify the clinical and the histological predictors of renal outcome.

METHODS

One hundred three patients with biopsy-proven LMN were diagnosed and followed in 2 Italian renal units (Ospedale Maggiore, Ospedale San Carlo in Milan) from January 1974 to December 2008. Of them, 67 had pure membranous nephritis (class V) and 36 mixed LMN (18 class V+III, 18 class V+IV). The clinical characteristics at presentation of this cohort are reported in Table 1. Six patients were lost to follow-up within a few months after renal biopsy, all with pure LMN. The mean follow-up of the other 97 patients was 156.5 + 104.5 months (median 139.2, 25th and 75th percentile, 70.6-228.8). All the patients but 6 were white.

The clinical course of these patients has been retrospectively evaluated.