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CLINICAL INVESTIGATION

Idiopathic membranous nephropathy: The natural history of untreated patients

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Idiopathic membranous nephropathy: The natural history of untreated patients. We reviewed the diagnostic features and clinical course of 140 patients with idiopathic membranous nephropathy who had their index renal biopsies performed at the Mayo Clinic between 1972 and 1984. There were 93 males and 47 females (average age, 50.8 ± 17 years); 116 patients (83%) had the nephrotic syndrome and 42 (30%) were hypertensive at diagnosis. Eighty-nine patients were not treated with corticosteroid or immunosuppressive drugs and 51 patients were treated mainly with short-term courses of prednisone alone; a minority of patients also received meclofenamate, cyclophosphamide, azathioprine, or chlorambucil. Five-year survival, including patients who received dialysis or a renal transplant, was 85%, 75% at 10 years, and no different from expected survival; there was no difference between untreated and treated groups. Also, there were no differences in the outcomes of renal function and protein excretion between untreated and treated patients. Among 28 patients (20%) who developed end-stage renal disease, 17 showed rapid progression within 2.5 years after diagnosis. Fifteen of the 17 patients were males; all were severely nephrotic and had impaired renal function at diagnosis. Only 1 of 24 patients with nonnephrotic proteinuria at index renal biopsy progressed to end-stage renal disease. Overall, a level of baseline proteinuria of 10 g or more per 24 hours and variable blood pressure control in hypertensive patients were associated with renal progression.

As a form of primary glomerulopathy with a well-defined histologic appearance, idiopathic membranous nephropathy is most common in adults with the nephrotic syndrome. Although there are distinctive morphologic and immunopathologic characteristics, the glomerular lesion most likely represents a constellation of different disease processes [1, 2].

Progression to renal failure varies widely in analyses of large numbers of both untreated and treated patients worldwide [3–12]. Variations in clinical course undoubtedly stem from poorly understood causes and pathogenesis. There are also recognized clinical observations of better outcomes, particularly in women [13], children [5], and those who have nonnephrotic proteinuria at presentation, as opposed to a worse prognosis in patients who present with the nephrotic syndrome [4, 7, 10]. Association of idiopathic membranous nephropathy with HLA DR3 has been found in populations from England, Germany, and Spain and with HLA DR2 in Japan [14, 15]. A benign clinical course has been reported in Japanese patients [15]. On the other hand, patients from England with the haplotype B18-BfF1-DR3 had a worse prognosis than others [14]. All of these conditions must be taken into consideration when evaluating the effects of various therapies on clinical outcome.

The treatment of idiopathic membranous nephropathy remains controversial [16, 17]. Eight prospective, controlled, clinical trials have been published, more than in any of the other primary glomerular diseases [18–25]. Four studies failed to show effectiveness of several treatments [18–21] and four reported beneficial effects [22–25].

We report our long-term observations on 140 patients with idiopathic membranous nephropathy, 89 of whom did not receive treatment with either corticosteroid or immunosuppressive drugs. Reviewing the natural history of idiopathic membranous nephropathy is particularly important in view of the unsettled issue of therapeutic intervention.

Methods

Selection of patients

Renal biopsies from 170 patients with membranous nephropathy who had their index biopsies at the Mayo Clinic between 1972 and 1984 were examined. To ensure a uniform approach to histologic diagnosis, tissue blocks of light microscopic sections and tissue for immunofluorescent- and electron-microscopy were prepared by standard techniques [26].

Staging of the glomerular morphology by electron microscopy followed that advocated by Ehrenreich and Churg [27] and Churg [28]. Each renal biopsy specimen was graded by two of us (M.O. and K.E.H.) without prior clinical knowledge of the case. When an inadequate or a nonrepresentative sample of glomeruli was available from the original electron microscopy studies, additional tissue was prepared for electron microscopic examination by using previously paraffin-embedded tissue. Final assignment of a given case to a certain stage represented a composite or sum of the most prominent lesions seen in the glomeruli examined. For example, in stage II and III lesions, small segments of basement membranes with few or no subepithelial deposits were commonly found with no or little alterations of the lamina densa. Also, occasional loops in a stage II

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lesion showed isolated deposits exhibiting reabsorption of deposits. More advanced stage IV lesions showed individual segments of capillary wall with stage I, II, or III lesions. In cases in which the given lesions of stages II and III or stages III and IV were equal, the assignment of the lesion was to the highest category.

Five stages of development were defined as follows:

Stage I. Small deposits were scattered along subepithelial surfaces of the basement membranes; there were focal confluence of deposits, an absence of rudimentary basement membrane reaction (spikes), and lamina densa of normal thickness.

Stage II. Large numbers of subepithelial deposits (many confluent) were located along most peripheral capillary loops; there were deposits indenting lamina densa and prominent spikes with infrequent incorporation of deposits.

Stage III. There was a large number of subepithelial deposits, prominent incorporation of deposits into thickened lamina densa, and reabsorption of deposits was well-defined.

Stage IV. Stage IV lesions showed markedly thickened lamina densa with variable electron densities and segments of basement membranes which may contain lesions of stage I, II, or III.

Stage V or end-stage. This had capillary wall collapse and global sclerosis with some loops showing lesions of stage I, II, or III.

In seven biopsies electron microscopic examination was not available so that staging of the glomerular lesion was based on assessment of the thin-section light microscopy.

Details of patients

The histories of those patients with histologically defined membranous nephropathy were reviewed. Twenty-four patients were excluded from study for the following reasons: systemic diseases of lupus erythematosus (6) and rheumatoid arthritis (6)—in the latter, associations with gold-salt treatment (3) and gold-salt plus D-penicillamine treatment (2); other disorders including crescentic glomerulonephritis superimposed on membranous nephropathy (2), bullous pemphigoid (2), lymphoproliferative disease (2), cryoglobulinemia (1), idiopathic thrombocytopenic purpura, Coombs'-positive hemolytic anemia, and IgG kappa monoclonal proteinemia (1), myasthenia gravis (1), polyarteritis nodosa (1), pyoderma gangrenosum (1), polymyalgia rheumatica and gold-salt treatment (1). Four patients with idiopathic membranous nephropathy were excluded from analysis because they presented with renal failure: three were dialysis dependent and one patient had a serum creatinine level of 8.2 mg/dl and progressed to dialysis treatment in four weeks. No follow-up information after renal biopsy was obtained for two patients. Thus, 140 patients with idiopathic membranous nephropathy comprised the study group. Patients were followed at varying intervals in this retrospective clinical review.

Baseline laboratory data at index renal biopsy were analyzed with respect to urinalysis, concentrations of serum creatinine, cholesterol and triglycerides, serum protein electrophoresis, serologies including hepatitis B surface antigen, antinuclear antibodies, CH_{50}, C3, 24-hour creatinine clearance (C_{Cr}) and total protein excretion, and clearance of iothalamate (C_{Iot}). Standard techniques of the Mayo Clinic clinical laboratories were used in each instance.

If recent clinical or laboratory data were not available from personal examination at the Mayo Clinic, a local physician or the patient was contacted to ascertain information that included determination of blood pressure; treatments used for hypertension, the nephrotic syndrome, and the glomerulopathy; and return of serum and 24-hour urine samples for measurement of C_{Cr} and total urine protein.

Among the 140 patients, 89 were not treated with corticosteroid, immunosuppressive, or other drugs. Fifty-one patients were treated as follows: prednisone alone (33), pre-index biopsy (13), and post-index biopsy (20). Prednisone was administered before or in combination with other drugs as follows: meclofenamate (9), oral cyclophosphamide (3), azathioprine (1), and chlorambucil (1). Meclofenamate was used in a prospective study of severe nephrotic syndrome that included nine patients in this review [29]. Nineteen patients were receiving prednisone at the time of their index renal biopsy. Minimal prednisone treatment was with 40 mg/day for one month in two patients; 18 received prednisone at a dosage of 60 mg/day for two months or longer, and the remainder of those who were given prednisone, either alone or combined with an immunosuppressive agent, took 20 to 40 mg/day for 6 to 24 months. Cyclophosphamide alone was given to four patients in a dosage of 2 mg/kg per day for one year [20].

Hypertension was treated with a wide variety of antihypertensive agents and sodium restriction, usually to less than 90 mEq/day, and various diuretic regimens were given for hypertension and control of edema.

Criteria for patient assessment

Particular attention was paid to certain arbitrarily defined criteria of outcome. For renal function: 1) stable (serum creatinine within 0.3 mg/dl from baseline); 2) renal insufficiency (serum creatinine, 2 to 5 mg/dl); and 3) renal failure (serum creatinine, >5 mg/dl). For proteinuria: 1) nephrotic syndrome (proteinuria, >3.5 g/24 hr, and lipiduria) or persistent proteinuria (>2 g/24 hr) and 2) remission of nephrotic syndrome (either partial [urine protein, 0.2 to 2 g/24 hr] or complete [urine protein, <0.2 g/24 hr]). For deaths, the date of death and cause were recorded and included a review of autopsy reports when available.

Data analysis

Clinical data forms were completed and the information was placed on magnetic tapes for analysis by using SAS (Statistical Analysis Systems) software. Data were then analyzed in the Section of Medical Research Statistics at the Mayo Clinic (D.M.I. and C.-P.C.). Patient and kidney survival were estimated by survivorship analysis by using the method of Kaplan and Meier [30]. The relationship of covariates to patient and to kidney survival was investigated univariately with the log-rank test [31], and multivariately with the Cox proportional-hazards model [32]. Sufficient data to test in the multivariate procedure included age, sex, systolic and diastolic blood pressure, serum creatinine, 24-hour urine protein, serum cholesterol, and triglyceride levels. Discrete variables were compared in untreated and treated groups with χ^2 tests, and continuous variables were compared with *t*-tests or with rank-sum procedures.

Table 1. Clinical features at index renal biopsy in 140 patients with idiopathic membranous nephropathy

Males	93
Females	47
Age *yr*	
Range	11–81
Mean (±SD)	50.4 ± 16.8
Median	54
24 patients (17%) < 30	
Duration of proteinuria *months*	
Range	0–540
Median	4
Newly discovered, 26 patients (19%)	
Nephrotic syndrome *no. of patients*	
116 (83%); baseline proteinuria >3.5 g/24 hr + lipiduria	
43 (31%) had baseline proteinuria >10 g/24 hr	
Hypertension (BP >150/90 mm Hg), no. of patients 42 (30%)	
Newly discovered (15 patients) to 20 yr duration	

Table 2. Composite histologic stage of index renal biopsies in 140 patients with idiopathic membranous nephropathy[a]

Composite histologic stage	Biopsies, no.	%
I	12	8.6
II	100	71.4
III	27	19.3
IV	1	0.7
V	0	0
Total	140	100

[a] Severe arterial/arteriolar sclerosis in 33 biopsies (24%)

Results

The clinical features of the 140 patients at index renal biopsy are listed in Table 1. There was a male to female ratio of 2:1; the average age was 50.4 ± 16.8 years, and 24 patients (17%) were less than 30 years old. One hundred sixteen of 140 patients (83%) had the nephrotic syndrome at presentation, including 43 patients (31%) whose baseline proteinuria exceeded 10 g/24 hour. Forty-two patients (30%) were hypertensive. One hundred twenty-four patients (89%) were followed from the time of index renal biopsy to current status (within the past 12 months), end-stage renal disease, or death. Follow-up information to current status was incomplete in 16 patients. For the entire study group, follow-up was 0.2 to 14.3 years (mean, 6.2 years; median, 6.1 years).

Histologic staging of the index renal biopsies is shown in Table 2. The majority of the biopsies were classified as well-developed or stage II lesions. To emphasize the overlapping found on electron microscopic examination, 66 biopsy specimens were further designated within major stages as 28 early and 31 late II lesions and 7 late III lesions.

Multiple clinical variables were analyzed between untreated and treated groups (Table 3) and were not significantly different for sex, age, duration of proteinuria, hypertension, stage of the index renal biopsy, or baseline laboratory findings, including serum creatinine level, C_{Cr}, C_{Iot}, 24-hour urine protein, or levels of serum albumin, total protein, and cholesterol. Mean serum triglyceride level was higher in treated patients ($P < 0.05$). As there were 19 patients receiving prednisone at the time baseline data were collected, the elevated triglyceride level relates to the effect of corticosteroids on increased lipoprotein production and reduced lipoprotein lipase activity mainly affecting very low density lipoproteins [33].

Table 3. Clincial variables at diagnosis in untreated and treated patients with idiopathic membranous nephropathy

Clinical features	Untreated $N = 89$	Treated $N = 51$
Sex, *M:F*	56:33	37:14
Age, *yr* (mean ± SD)	50.8 ± 17	49.7 ± 17
Median duration of proteinuria *months*	3	5
Blood pressure *mm Hg*		
Systolic (mean ± SD)	143 ± 23	142 ± 20
Diastolic (mean ± SD)	86 ± 12	87 ± 10
Stage of index renal biopsy	No. (%)	No. (%)
I	7 (8)	5 (10)
II	64 (72)	36 (71)
III	17 (19)	10 (20)
IV	1 (1)	0 (0)
Total	89 (100)	51 (100)
Laboratory findings (mean ± SD)		
Serum creatinine *mg/dl*	1.3 ± 0.6	1.2 ± 0.5
C_{Cr} *ml/min 1.73 m²* ($N = 43$)	84 ± 39	80 ± 29
C_{Iot} *ml/min 1.73 m²* ($N = 62$)	75 ± 31	81 ± 30
Proteinuria *g/24 hr*	8.2 ± 5.2	8.7 ± 6.1
Serum		
Albumin *g/dl*	2.3 ± 0.6	2.2 ± 0.7
Total protein *g/dl*	5.3 ± 0.8	5.1 ± 0.8
Cholesterol *mg/dl*	373 ± 124	400 ± 122
Triglycerides *mg/dl*	228 ± 149	279 ± 162[a]

[a] $P < 0.05$

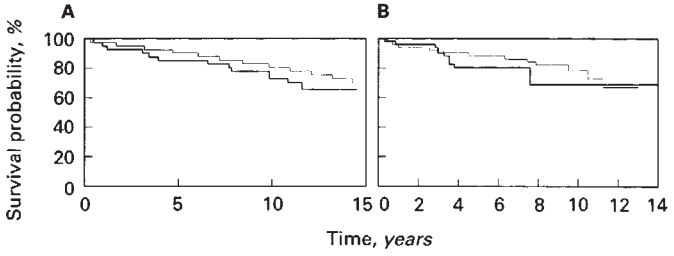

Fig. 1. *Survival of patients with idiopathic membranous nephropathy.* **A.** Comparison with survival of age- and sex-matched upper midwest (Life table) population. Symbols are: (—) Life table population; (—) all patients. **B.** Comparing untreated (—, $N = 89$) and treated patients (—, $N = 51$).

Patient survival for the total, the untreated, and the treated groups is shown in Figure 1. The overall survival was 85% at 5 years and 75% at 10 years; these were not significantly different from normal, and there was no significant difference between nontreatment and treatment groups. Survival without death or renal failure was 71% at 5 years, 58% at 10 years, and although about 10 percentage points higher in untreated patients, not significantly different from the treated group (Fig. 2).

The outcome of renal function according to criteria based on serum creatinine data shows no significant differences in the categories of stable, end-stage renal disease, or renal insufficiency outcomes between untreated and treated groups (Table 4). Overall, for the 140 patients, 90 (64%) remained stable, 28

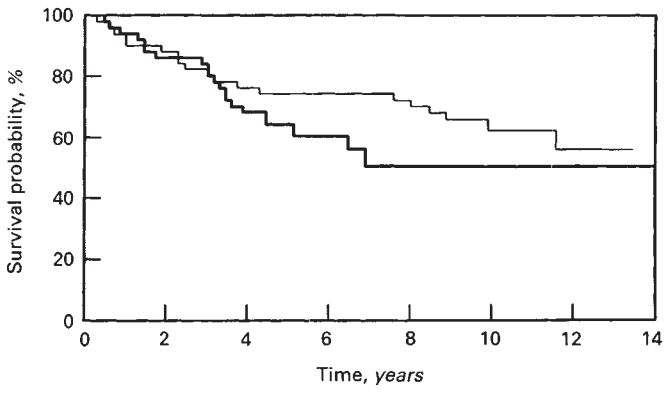

Fig. 2. *Survival without death or renal failure in untreated (—, N = 89) and treated (—, N = 51) patients with idiopathic membranous nephropathy.*

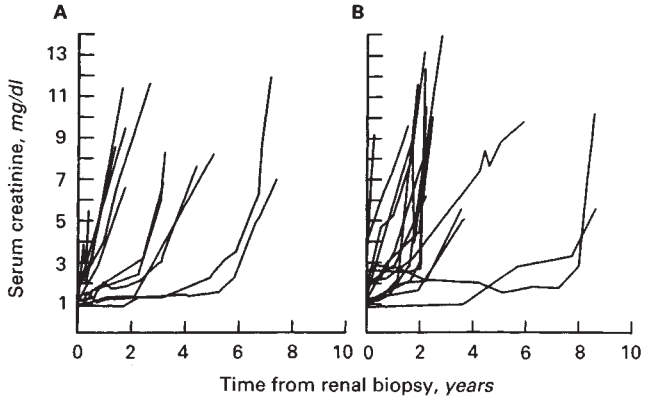

Fig. 3. *Serum creatinine over time for the 28 patients who developed end-stage renal disease, 17 of whom (A 6 treated and B 11 untreated) showed progression within 2.5 years after their index renal biopsy.*

Table 4. Outcome of renal function by serum creatinine data in untreated and treated patients with idiopathic membranous nephropathy

Group	Stable no. (%)	Serum creatinine: End-stage renal disease, >5 mg/dl no. (%)	Serum creatinine: Renal insufficiency, 2-5 mg/dl no. (%)
Untreated $N = 89$	60 (67)	16 (18)	13 (15)
Treated $N = 51$	30 (59)	12 (24)	9 (18)
Total	90 (63)	28 (21)	22 (16)

Table 5. Variables at renal biopsy index associated with rapid progression to end-stage renal disease

	Rapid progressions $N = 17$	Rest of group $N = 123$	Significance
Sex *M:F*	15:2	78:45	<0.05[a]
24 hr Proteinuria *g*	14.8 ± 8	7.5 ± 4.5	<0.001[b]
Serum			
Creatinine *mg/dl*	1.8 ± 0.9	1.2 ± 0.4	<0.001[b]
Cholesterol *mg/dl*	463 ± 120	369 ± 119	<0.01[b]
Triglycerides *mg/dl*	304 ± 173	234 ± 149	<0.05[b]

[a] χ^2 test
[b] Two-sample *t*-test

(20%) developed end-stage renal disease, and 22 (16%) had renal insufficiency at last analysis. The time course to renal failure found by plotting serum creatinine values from baseline to end-stage renal disease (first serum creatinine level >5 mg/dl) was not different comparing untreated and treated groups. In the 16 untreated patients, the time course to end-stage renal disease was 3.9 ± 1.4 years and in the 12 treated patients it was 3.2 ± 0.8 years.

For the 28 patients who progressed to end-stage renal disease, the values for serum creatinine over time are plotted in Figure 3. In 17 patients (11 untreated, 6 treated) progression to end-stage renal disease occurred in 2.5 years or less after index renal biopsy. Clinical variables associated with this rapid progression were male gender, elevated serum creatinine levels, and nephrotic syndrome (24-hour urine protein, serum cholesterol, and triglycerides) (Table 5). There were no significant differences between untreated and treated groups. We did not find an association between rapid progression and age, stage of the index renal biopsy, baseline systolic and diastolic blood pressures, serum proteins, C_{Cr}, or C_{Iot}. Renal function by clearance measurements were made in fewer patients than were estimates by serum creatinine determinations. In the 11 patients with more gradual progression to end-stage renal disease, six were males, five were females, and all were nephrotic at presentation and throughout their clinical course.

By multivariate analysis, serum creatinine and 24-hour urine protein levels ($P < 0.01$) and serum triglyceride concentrations ($P < 0.03$) remained significantly associated with progression to end-stage renal disease.

Table 6. Outcome of proteinuria at last follow-up in 116 patients with nephrotic syndrome and idiopathic membranous nephropathy

Group	Patients[a] no. (%)
Untreated, $N = 72$	
Remission	41 (57)
Persistent proteinuria	7 (10)
Nephrotic syndrome	24 (33)
Treated, $N = 42$	
Remission	17 (40)
Persistent proteinuria	5 (12)
Nephrotic syndrome	20 (48)

[a] Nephrotic syndrome was intermittent in 17 patients (15%) with various outcomes, including 8 nephrotics, 7 remissions, and 2 with nonnephrotic proteinuria. Urine protein was not quantified for 24-hour measurement in 2 untreated patients so that follow-up information to last analysis is available in 114 patients.

The outcome of proteinuria in the 116 nephrotic patients as judged by the defined criteria for patient assessment showed no differences in the nontreatment and treatment groups (Table 6). The majority, or 41 of 72 (57%), of untreated patients and 17 of 42 (40%) treated patients had achieved either partial or complete remission from the nephrotic syndrome at final assessment. The nephrotic syndrome was intermittent in 17 patients

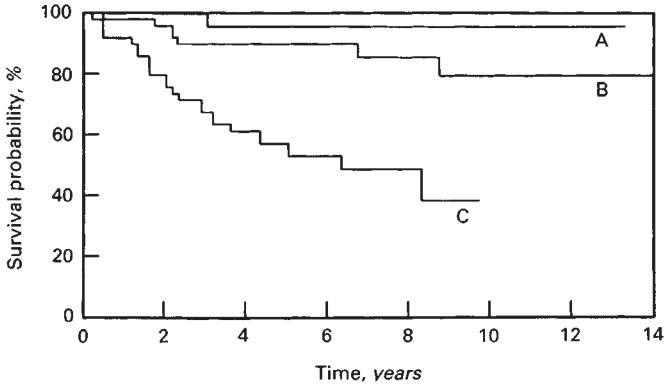

Fig. 4. *Probability of surviving without developing end-stage renal disease according to baseline proteinuria: group A, 24 patients, 0-3.4 g/24 hr; group B, 73 patients, 3.5-10 g/24 hr; and group C, 43 patients, 10 or more g/24 hr ($P < 0.0001$).* A vs. B (NS), A vs. C ($P < 0.001$), and B vs. C ($P < 0.0001$).

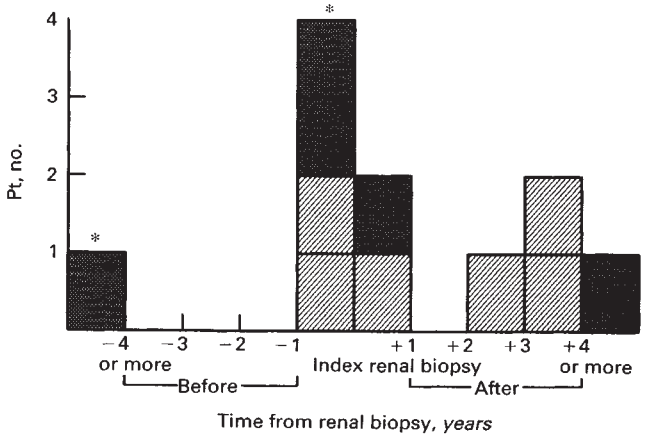

Fig. 5. *Timing of diagnosis of malignant disease before and after date of index renal biopsy in patients with idiopathic membranous nephropathy.* *One patient (untreated group) had small cell carcinoma of the lung diagnosed 4 years before, and a second primary, squamous cell carcinoma of the lung diagnosed simultaneously with index renal biopsy. Symbols are: (▨) treated; (■) untreated.

(15%) who had various outcomes for proteinuria (Table 6), and proteinuria was variable in 7 (29%) of the 24 patients with baseline nonnephrotic proteinuria. In the nonnephrotic group, 13 of 15 untreated patients and 4 of 9 treated patients were in partial nephrotic remission, 5 treated patients had nephrotic-range proteinuria, and, at last measurement, 2 untreated patients had persistent proteinuria (2.9 g/24 hr). These data indicate the high degree of variability of proteinuria in idiopathic membranous nephropathy when this continuous variable is analyzed long term.

Progression to end-stage renal disease was associated with a level of baseline proteinuria of 10 g or more per 24 hours (Fig. 4). By survival analysis, the probability of surviving without renal failure was significantly worse when intervals of proteinuria were compared among the nonnephrotic range (0 to 3.4 g/24 hr) and the midnephrotic range (3.5 to 10 g/24 hr) and the severe nephrotic range (10 or more g/24 hr). Only one patient with proteinuria in the nonnephrotic range became persistently nephrotic and developed end-stage renal disease, whereas two others (one untreated and one treated) had renal insufficiency (serum creatinine 2 to 5 mg/dl range) at last follow-up.

Variable blood pressure control in hypertensive patients throughout the clinical course was related to a higher progression rate defined as the development of end-stage renal disease or a doubling of serum creatinine level from baseline (Table 7) ($P < 0.05$, log-rank test). No difference in the relationship of hypertension and renal progression was noted between the untreated and corticosteroid- or immunosuppressive-treated groups.

Various cancers were found in 10 of 140 patients (7.1%), including six in the treated and four in the untreated groups. The relationship between diagnosis of the malignancies and the index renal biopsies is shown in Figure 5.

Twenty-five of 140 patients (18%) died. Sixteen deaths were nonrenal related—10 in the untreated and 6 in the treated group. There were various causes of death: carcinomas (7), cardiovascular (5), and miscellaneous (4). Nine patients died after renal failure was established. In five untreated patients, four had been on long-term dialysis and died of the following: *Staphylococcus* sepsis (2), with seizures in one; cardiac arrhythmia (1); and cerebrovascular accident (1). One uremic male patient died without support of his renal failure. Four treated patients died, two after being established on dialysis programs, and both after surgery: one from an acutely perforated duodenal ulcer and the other from an ischemic bowel. Two patients died after renal transplantation, one from a ruptured ventricular aneurysm within six months after allografting and a second two years after transplant from acute hepatic necrosis due to recurrent HBs antigen-positive hepatitis.

Discussion

These 140 patients with idiopathic membranous nephropathy had characteristics of male predominance, an average age of 50 years, the nephrotic syndrome in 116 (83%), and hypertension in 42 (30%) when their renal morphologic diagnosis was established. Eighty-nine patients were not treated with corticosteroid or immunosuppressive drugs and 51 patients received mainly short-term treatment with prednisone, usually in a dosage of 60 mg/day for two months. A minority of treated patients also was given meclofenamate or an immunosuppressive agent (mostly cyclophosphamide). The clinical characteristics between untreated and treated patients were similar except for higher serum triglyceride levels in the steroid-treated patients.

Five-year and 10-year patient survival rates were not significantly different from expected survival nor were they different between untreated and treated groups. Furthermore, survivorship without death or end-stage renal failure combined was similar between untreated and treated patients. We also emphasize that the overall outcomes of renal function and proteinuria were not different between untreated and treated patients, and more than one-half of the patients were in either partial or complete nephrotic remission and had stable renal function at final follow-up. In this retrospective analysis, the different therapeutic regimens may have biased the long-term ineffectiveness of treatment that we observed. An obvious point to underscore here is that treatment effects can only be truly evaluated in well-designed, prospective clinical trials.

Table 7. Hypertension at index renal biopsy and blood pressure control related to renal progression in untreated and treated patients with idiopathic membranous nephropathy

Group	Hypertensive no.	Renal progression[a] no.	%	Normotensive no.	Renal progression[b] no.	%
Hypertension at baseline						
Untreated	31	10	32	58	8	14
Treated	23	6	26	28	6	21
Total	54	16	30	86	14	16
Blood pressure control in hypertensive group						
	Adequate[c]			*Variable*		
Untreated	17	4	24	14	6	43
Treated	17	2	12	6	4	67
Total	34	6	18	20	10	50

Hypertensive vs. normotensive progression, $P = 0.08$ (log-rank test); adequate vs. variable progression, $P < 0.005$ (log-rank test).
[a] Doubling serum creatinine level from baseline only (1); end-stage renal disease only (7); doubling serum creatinine + end-stage renal disease (8)
[b] Doubling serum creatinine level from baseline only (1); end-stage renal disease only (7); doubling serum creatinine + end-stage renal disease (6)
[c] Average blood pressure = 140/85 mm Hg or lower.

In analyzing variables at the time of the index renal biopsy, we identified a subset of patients who were at high risk for a rapid progression to end-stage renal disease occurring within 2.5 years after biopsy. These risks were male sex, elevated serum creatinine level, and nephrotic syndrome with an average urine protein excretion of 14.8 g/24 hr. There was a significant correlation between renal progression and increasing levels of baseline protein excretion. Hypertensive patients whose blood pressure was variably controlled had more progressive renal disease. Also, the issue of renal vein thrombosis was addressed in 27 patients included in this review in a previously reported prospective study in which no differences were found in renal progression between those with and without renal vein thrombosis [34].

Concerning the favorable outcomes, the information provided in our review is quite similar to that recently reported in three other series of large numbers of patients with idiopathic membranous nephropathy that included those who were untreated [7, 11, 12]. In the study with the largest number of untreated patients, Noel et al [7] reported that only 10 of 116 patients (9%) developed end-stage renal disease of a total of 22 (19%) who had impaired renal function after an average follow-up of 4.5 years. The low incidence of end-stage renal disease is partly attributed to an inherently improved prognosis found in their population that consisted of nearly 50% females and younger patients, with 25% less than age 20 years at diagnosis. The nephrotic syndrome was present in 76% of the patients at onset. In the two other studies, actuarial 10-year survival rates were 90% in a report from Japan [11] and 83% in a study from Finland [12]. Sixty percent of the Japanese and 75% of the Finnish patients were nephrotic at onset of disease. In both of these studies, there were no differences in patient survival or renal function outcomes between untreated patients and those treated with corticosteroids alone or combined with cyclophosphamide [11, 12]. Previously reported long-term clinical reviews [3–6, 8], including one of our own [4], also showed that a majority of patients, regardless of treatment (primarily with glucocorticoids), survived without terminal renal failure. The cumulative results from all of these studies further support the contention that patients with idiopathic membranous nephropathy have as good a prognosis irrespective of corticosteroid therapy, with or without cyclophosphamide, the predominant cytotoxic drug used, or no treatment other than control of high blood pressure.

Treatment with corticocosteroids or immunosuppressive drugs or both is supported best in two published clinical trials [23, 25] conducted in nephrotic subjects but not necessarily a high-risk population. Renal function was stabilized by the use of alternate-day prednisone treatment (100 to 150 mg in a single dose on alternate days for 2 months) in the collaborative study of the adult nephrotic syndrome [23] and therapy with methylprednisolone (1 g intravenously for three days, then the oral preparation at 0.4 mg/kg per day or prednisone 0.5 mg/kg per day) followed by chlorambucil (0.2 mg/kg per day) in monthly cycles for six months in the Italian multicenter trial [25]. Also, in the Italian trial, remissions from the nephrotic syndrome occurred more often in the treated than in the control group in patients primarily with stage I and II lesions [25]. Replications are lacking for both of these treatment modalities, although two trials of alternate-day prednisone treatment are under way in Canada [35] and the United Kingdom (Cameron JS, personal communication). In the Canadian trial, treatment with prednisone, 45 mg/m^2 on alternate days for six months, is being compared with controls. In a preliminary report, equal numbers of patients in the treated and control groups had developed end-stage renal disease, but renal function, as assessed by creatinine data, appeared to be more stable in treated patients with stage I and II glomerular lesions [35]. There are no details from the United Kingdom study. Incidentally, we found no relationship between remission rates or progressive renal disease and the composite stage of index renal biopsies.

A major concern in the two fully reported clinical trials is what appears to be a higher than expected progression rate in the control groups. Because of a relatively short follow-up period of two to three years, the continuous variable of a doubling rate of serum creatinine [23] or change in the reciprocal of the plasma creatinine levels [25, 36] was the determinant used for effects of treatment on renal function. A comparison of renal progression by change in serum creatinine level can be made between untreated nephrotic patients in the studies by Noel et al [7] and the present study and control populations in the clinical trials (Table 8). For patients at risk after two years,

Table 8. Loss of renal function determined by a doubling of serum creatinine level in nephrotic patients with idiopathic membranous nephropathy after 2 years of treatment versus placebo or control and nontreatment

Study	Treatment	Patients in whom serum creatinine doubled after 2 years		
		No. at risk	No.	%
Noel et al [7 and 23]	Nontreatment	59	7	12
Collaborative Study [23]	Alternate-day prednisone	20	2	10
	Placebo	25	11	44
Ponticelli et al [36]	Methylprednisolone + chlorambucil	34	1	3
	Control	31	7	23
Present study	Nontreatment	74	9	12

the serum creatinine level doubling rates were nearly two times higher in the controls in the Italian trial [36] and almost fourfold higher in the placebo group in the collaborative study [23], compared with those found by Noel et al [7] and ourselves in untreated patients. Moreover, the doubling rates were comparable between alternate-day prednisone-treated patients in the collaborative trial [23] and untreated patients in the report of Noel et al [7] and in our results. The combined methylprednisolone and chlorambucil-treated group in the Italian multicenter trial [36] had a somewhat lower progression than was demonstrated in untreated patients. However, the long-term effects of this combination of treatments on progression to end-stage renal disease is not known at this time because of a relatively short follow-up period. The major message in the above comparison, however, is to show that the favorable effect of treatment on renal function in the clinical trials may be apparent because of the relatively high progression rates that were observed in their control groups.

Final consideration is given to the identification of risk factors in patients who had progressive loss of renal function. Both in our review and in that of Davison et al [10], the deterioration of renal function was largely distinguishable from those with stable renal function after approximately 2.5 years. Furthermore, Davison et al [10] identified similar risks to ours that were associated with rapid progression, which included severely nephrotic males who had impaired renal function at the time of diagnosis. Slower progression rates, in our study and in that of Davison et al [10], were found in a smaller group of patients with persistent nephrotic syndrome. In the study by Kida et al [11], a steady state was reached in the distribution of patients who remained nephrotic and those who were in remission from the nephrotic syndrome after five years. The majority who were in nephrotic remission had stable renal function thereafter, as also demonstrated in our patients who entered remission.

Evidence of malignancy in 7.1% of our patients is no greater or less than that reported in patients with membranous nephropathy in the medical literature [37]. The association between carcinomas and membranous lesions is presumably mediated by immune complexes comprised in part of tumor-associated antigens [1, 2, 37]. We can say nothing further about the reported association between malignancies and membranous nephropathy other than to refer to an analysis of another purported association between a paraneoplastic condition, polymyositis-dermatomyositis, and malignancy. Lakhanpal and associates [38] reported that patients with polymyositis-dermatomyositis had more malignant disease (25%) than the carefully matched control population (17%), but that the difference was not statistically significant. The slight excess of cancer seen among all the patients was contributed to by the most distant referral and may best be explained on the basis of referral bias. This study was also conducted at the Mayo Clinic and included patients from the approximate geographic area from which our patients were derived. Thus, by inference, our frequency of 7.1% is actually lower than the 17% found by Lakhanpal and associates [38] in their control population.

Our clinical review supports the recent studies that showed normal patient survival and low renal progression rates in various populations of patients with idiopathic membranous nephropathy. Furthermore, we identified a subset of high-risk patients who progressed to renal failure in a relatively short time. It is in these readily identifiable patients that prospective clinical trials should be undertaken to test encouraging new therapies.

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