

A STUDY OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS IN IRAN

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Background: The aim of this study was to review the morphologic patterns of membranoproliferative glomerulonephritis (MPGN) in 100 Iranian patients using light microscopy (LM) and electron microscopy (EM), and to compare the treatment and outcome in 13 patients with two biopsies.

Patients and Methods: A retrospective study of 713 kidney biopsies of Iranian patients received between 1981 to 1994 was carried out. Of the 713 kidney biopsies, MPGN (n=106) and membranous glomerulopathy (n=112) made up the highest numbers of cases.

Results: Among 100 MPGN patients, 55 (55%) were MPGN type I, 10 were type II (10%), and 35 type III (35%). Eighty-three (83%) had nephrotic proteinuria, 39 (39%) had hematuria, and 52 (52%) were hypertensive. Complement levels were estimated in 58, with low C3 in 10. The glomerular involvement was irregular, with focal hypercellularity in 47 patients (47%), widely patent capillaries in 50 (50%), arteriosclerosis in 48 (48%), and with hyaline change in 25 (25%). Follow-up data (22-130 months) was available in 61 (61%) patients: 6 (10%) died after 14-56 months, 27 (44%) were on maintenance hemodialysis for 15-110 months, and three received transplants. Thirteen patients had detailed follow-up and a second biopsy after 24-120 months. All 13 presented with edema and nephrotic range proteinuria, with hematuria and hypertension in five and azotemia in four. Seven of the 13 patients received initial steroids, followed by antiplatelet or antihypertensive drugs. Four (type III) patients received antiplatelet and antihypertension drugs, and two (type III) received only antihypertensive drugs. In the first biopsy, glomerular changes by light microscopy were non-uniform in 7 of 10 (70%) type III MPGN cases. Vascular changes were absent or mild in 11, and moderate in two. In the second biopsies, 10 showed decrease in cellularity, with many open capillaries, persistence of deposits by EM in all, and progression of vascular sclerosis in eight, and tubulointerstitial changes in 10. Among the 13, six were clinically stable, another six received dialysis followed by transplant in three, and one had relapses with episodes of cryoglobulinemia. Three patients died.

Conclusion: There is a high incidence of MPGN in Iranian patients, with a substantial number of type III MPGN cases. Second biopsies showed decreased cellularity, but increase in chronic tubulointerstitial and vascular cases. Steroids did not appear to benefit the outcome in types I and III MPGN patients compared to patients who received antihypertensive and antiplatelet treatment without steroids.

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Membranoproliferative glomerulonephritis (MPGN) is a chronic, slowly progressive glomerular disease, characterized by a distinct morphologic pattern. Based on the histologic pattern, it may be referred to as lobular glomerulonephritis,^{1,2} mixed membranous and proliferative glomerulonephritis,³ membranoproliferative glomerulonephritis,⁴ or mesangiocapillary glomerulonephritis.² Based on the clinical findings, it may also be referred to as

hypocomplementemic glomerulonephritis. The disease mainly affects adolescents or young adults who present with nephrotic range proteinuria and/or hematuria, however, presentation varies from incidental gross hematuria and/or proteinuria, sometimes associated with upper respiratory infection, acute nephritic syndrome, to insidious onset of edema due to nephrotic syndrome. Thus, a definite diagnosis of MPGN can only be established by evaluation of kidney biopsy by light microscopy (LM), electron microscopy (EM) and immunofluorescence microscopy (IM). Although the course of the disease is characterized by remissions, it almost always progresses to end-stage disease, with hypertension as an inevitable complication. Treatment is often unsatisfactory,⁷⁻¹⁰ however, some studies suggest encouraging results,¹¹ with

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intermittent steroid therapy,^{7,8} cyclophosphamide and with anticoagulants.⁹

The LM features of MPGN include glomerular enlargement with hypercellularity, inflammatory cell infiltration, and widening of mesangia, with increase in matrix and cells, resulting in simplification of tufts, with a “membranoproliferative” or “lobular” appearance, and with “tram tract” or “double contour” patterns. Based on the location of deposits by EM, three subgroups of MPGN, namely type I, II, and III are recognized.¹²⁻¹⁷ In all three types of MPGN, subendothelial and often mesangial deposits, and mesangial extension are present in EM. In type III MPGN, the glomeruli are often less cellular, with many patent capillaries, and segmental double-contour pattern. By EM, subepithelial deposits of varying size, hump-like deposits, or a “membranous” pattern with basement membrane spiking is seen. By IM in all three types of MPGN, granular deposits of C3 are seen along the glomerular capillary walls and in the mesangium. Immunoglobulins, especially IgG, often accompany C3 in type III, and sometimes in later stages of the disease in type I MPGN.

In this study we present the clinical data and histologic types of MPGN in 100 patients, and describe in detail the histologic findings of 13 patients with two biopsies, and discuss the outcome of treatment.

Materials and Methods

Over a span of 13 years, 713 kidney biopsies of Iranian patients were received from Iran. The biopsies came from one institution in Tehran (capital of Iran), and include local as well as referred patients from various parts of Iran. Among the various diseases, MPGN (n=106) and membranous glomerulopathy (n=112) had the highest number of cases, followed by lupus nephritis (90), minimal change disease (81) and amyloidosis (23) (Table 1).

A retrospective study of 106 patients with membranoproliferative glomerulonephritis (MPGN) was carried out, of which 100 cases were selected. These comprised 55 males and 45 females. About 76% were between ages 11 and 40 years. The youngest patient was one year old and the oldest was 65 years. In 13 patients, follow-up biopsies were available for review, therefore, a total of 113 biopsy specimens were reviewed. All patients were of Iranian descent. Eleven were between the ages of 1 and 10 years, 36 were between 11 and 20 years, 22 between 21 and 30 years, 18 between 31 and 40 years, and 13 were above 40 years.

The biopsies were fixed in Zamboni's fixative, and were studied by LM and EM. For LM, hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), Masson's trichrome stain and periodic acid methenamine silver (PAMS) stains were used routinely. Transmission electron microscopy was performed on all biopsies using

conventional methods. Tissue was not available for immunofluorescence microscopy.

Results

At presentation, 83 out of 100 patients (83%) had nephrotic range proteinuria, 39 (39%) had hematuria, and 52 (52%) were hypertensive. Serum complement levels were available in 58, were low in 10, and among these 10 patients, three were blood-related.¹⁶ Antistreptolysin-O (ASO) test was performed in 55, and in five the titer was slightly elevated. One patient was noted to have dermal leishmaniasis. Serologic tests for systemic lupus erythematosus were performed in 74 patients and were negative in all. Serologic tests for hepatitis B were negative in 97, positive in one, and not tested in two, and for hepatitis C serology were negative in one and not tested in the rest.

The glomeruli were evaluated for uniformity of involvement, cellularity, inflammatory cell infiltration, presence of open capillaries, crescents, double-contours or tram-track patterns. The tubulointerstitial components were evaluated for chronic changes and the vessels for sclerosis and/or hyaline change using semiquantitative methods. The

TABLE 1. Distribution of Iranian cases by disease categories (n=713).

MPGN	106	MCD	81
MPGN-I	61	Focal segmental GS	48
MPGN-II	10	IgM nephropathy	5
MPGN-III (Hepatitis 1)	35	Mesangial glomerulopathy—unclassified	16
Membranous glomerulopathy	112	Hereditary nephropathy	17
Secondary MG	21	End-stage kidney	5
MG with RVT	4	Congenital nephrotic syndrome	4
Postinfectious GN	14	Tubulointerstitial disease (TID)	8
Postinfectious GN subsiding	6	ATN	1
Lupus nephritis (LN)	90	NSAID (TID+MCD)	4
Proliferative LN	63	Lymphoma infiltrates	2
Membranous LN	17	Sarcoid granuloma	1
Mesangial LN	10	Diabetic nephropathy	3
Immune complex GN	15	Myeloma/light chain disease	2
Focal proliferative glomerulonephritis (Weg 1, PAN 4, Cres 3)	22	Amyloidosis	23
Henoch-Schönlein purpura	6	Transplant biopsies	7
IgA nephropathy	9	Arterial and arteriolar sclerosis	19
Endocarditis-associated GN	1	Hemolytic uremic syndrome	3
Immunotactoid nephropathy	2	Tissue inadequate	64
		Normal renal biopsy	17
Total	383	Total	330

Weg=Wegener's granulomatosis; PAN=polyarteritis nodosa; Cres=crescentic glomerulonephritis; GS=glomerulosclerosis; ATN=acute tubular necrosis; RVT=renal vein thrombosis; MCD=minimal change disease; NSAID=non-steroidal anti-inflammatory drugs.

same criteria used for LM were used in EM evaluation, and in addition, location and type of deposits were documented. Among the 100 biopsies, 55 (55%) were classified as type I MPGN, 10 (10%) as type II MPGN, and 35 (35%) as type III MPGN. Light microscopic changes in the 100 Iranian cases showed irregular glomerular involvement with focal hypercellularity in 47 (47%), and widely patent capillaries in 50 (50%). Arteriolar sclerosis was present in 48 cases (48%), with hyaline change in 25 (25%). By EM, subendothelial deposits were seen in all 100 biopsies, and mesangial deposits in 69 (69%). In 35 patients (35%), subepithelial deposits in addition to subendothelial and mesangial deposits were seen. In none of the biopsies were tubuloreticular structures present.

Follow-up information on the clinical course of 61 patients was available after a period ranging from 22 to 130 months. Of the 61 patients, 23 (38%) continued to have nephrotic range proteinuria, 18 (29%) were hypertensive, and 27 (44%) were on maintenance hemodialysis 15 to 110 months after diagnosis. Six (10%) patients died, two of sepsis (one during initial admission and another after 10 months), a third patient died after 14 months due to hypertension, and the remaining three died within 18-27 months of complications of end-stage renal disease (ESRD) and dialysis. Thirteen of 61 patients underwent a second biopsy, and had complete follow-up information (Table 2).

At initial presentation, all 13 patients had nephrotic range proteinuria, ranging between 3.6 to 18.8 g/day. Nine

patients also had hematuria (5 with numerous RBCs, and 4 with more than 10 RBCs per high-power field). Five patients were hypertensive, and four had elevated serum creatinine levels ranging from 1.5 to 4.5 mg/dL. The complement levels were normal in 11, and low in two. Serologic tests for systemic lupus erythematosus and syphilis were negative in all. ASO titers were minimally elevated in five. One patient was diagnosed with cutaneous leishmaniasis. All thirteen patients had negative serology for hepatitis B and one was also negative for hepatitis C. Serologic tests for hepatitis C were not performed in the remaining 12 patients.

Case Analysis

The morphologic changes in the first biopsies of the two MPGN type I patients (Table 2) showed uniform glomerular involvement with a lobular pattern, subendothelial mesangial extension, and mesangial and subendothelial deposits by EM. Both patients were treated with steroids followed by antiplatelet therapy (aspirin and dipyridamole). Both underwent second biopsies three years later, and one showed decreased glomerular cellularity, and widely patent capillaries. In both patients, there was persistence or increase in mesangial matrix resulting in areas of solidification, and vascular sclerosis associated with chronic tubulointerstitial disease. One patient (case #2) was started on maintenance hemodialysis four years after the second biopsy and died three years later. The other patient (case #12) received renal transplant three years after the second biopsy.

The glomerular changes in the MPGN type II patient (case #13) varied slightly and showed lobular pattern with ribbon-like, intramembranous, mesangial and occasional subendothelial deposits. The patient received prednisone followed by antiplatelet therapy. The second biopsy was performed two years later and showed decrease in cellularity, increase in mesangial matrix (sclerosis), and minimal increase in vascular and chronic tubulointerstitial disease. The patient remained stable with a creatinine level of 2.2 mg/dL.

In all 10 MPGN type III patients (cases 1, and 3 to 11), the morphologic changes in the first biopsy showed irregular glomerular involvement, however, it was moderate to marked in seven (Figure 1). Glomerular hypercellularity was noted in eight, patent capillaries in seven, and subendothelial mesangial extension, subendothelial mesangial and subepithelial deposits by EM in all (Figure 2). Second biopsies were performed two to 10 years later. In nine, the glomerular capillaries were open, and six showed increase in mesangial matrix (sclerosis) (Figures 3 and 4). The vascular and tubulointerstitial changes progressed in five patients. Two patients received steroid and antihypertensive therapy. One of these two died one year after the second biopsy, and the other had relapses with evidence of cryoglobulinemia. Another two received

TABLE 2. Treatment and outcome in 13 patients with two biopsies.

MPGN type	Case no.	Treatment group and drugs	Clinical outcome
I	2	A (Steroid+antiplatelet)	Dialysis 4 years after biopsy #2 Died 3 years later
I	12	A (Steroid+antiplatelet)	Transplant 3 years after biopsy #2
II	13	A (Steroid+antiplatelet)	Stable
III	1	A (Steroid+anti-HPN)	Died 1 year after biopsy #2
III	4	A (Steroid+antiplatelet)	Stable but lost to follow-up
III	8	A (Steroid+anti-HPN+azathioprine)	Relapses with cryoglobulinemia
III	9	A (Steroid+antiplatelet)	Dialysis two years after biopsy #2 Transplant for 4.5 years; died of sepsis
III	5	B (Antiplatelet+anti-HPN)	Stable
III	6	B (Antiplatelet+anti-HPN)	Dialysis 2 years after biopsy #2
III	10	B (Antiplatelet+anti-HPN)	Stable
III	11	B (Antiplatelet+anti-HPN)	Stable
III	3	B (Anti-HPN)	Transplant 1 year after biopsy #2
III	7	B (Anti-HPN)	Stable

Group A=steroids+other medication (antiplatelet or antihypertensive [HPN] drugs); Group B=antiplatelet and/or antihypertensive drugs only.



FIGURE 1. Case 8, Biopsy #1. Glomerulus is cellular and shows irregular involvement and lobular simplification (H&E, 80x).



FIGURE 2. Case 8, Biopsy #1. Portion of glomerulus shows subendothelial mesangial extension and subendothelial deposits (arrow). Small mesangial and many subepithelial deposits are present (arrowhead). There is diffuse effacement of epithelial foot processes (EM, 20,000x).



FIGURE 3. Case 8, Biopsy #2. Glomerulus shows marked decrease in cellularity, many open capillaries, rare inflammatory cells and increase in mesangial matrix (Toluidine blue, 80x).



FIGURE 4. Case 8, Biopsy #2. In comparison to the first biopsy, the changes are minimal, with many open capillaries, rare deposits (arrows) and increase in mesangial matrix (EM, 3000x).

steroids and antiplatelet drugs; one was stable but was lost to follow-up, and the other required dialysis two years following the second biopsy and received transplant 4.5 years later and died due to sepsis. Six patients did not receive steroids. Among these six, four received a combination of antiplatelet and antihypertensive regimen. Three remained stable and one required dialysis two years after the second biopsy. The remaining two received only antihypertensive drugs, one remained stable and the other received transplant one year after the second biopsy.

Discussion

The single unifying factor in the three subtypes of MPGN is the morphologic pattern by LM, and for further classification, EM and IM are necessary. In addition, the morphologic changes in types I and III MPGN are not unique to idiopathic MPGN, but can occur with autoimmune diseases, bacterial, protozoal and viral infections, and in neoplastic disorders.¹⁷⁻²⁰ The exact incidence of any glomerulonephritis is difficult to establish,

however, the high incidence of MPGN in non-industrialized countries²¹ could be explained in part by the large number and diversity of infectious diseases in these countries. The histologic pattern of "secondary" MPGN is quite similar to type I, and more so in type III MPGN.²² Thus, detailed clinical history and laboratory evaluation for underlying causes is of great importance. In addition, morphologic changes, such as tubuloreticular structures (e.g., lupus nephritis, hepatitis) and morphology of deposits, such as in cryoglobulinemia, should be carefully evaluated.

Among the 13 patients described, 10 were of type III MPGN. A history of preceding illness was present in seven, and ASO titer was slightly elevated in five patients (38%). Hepatitis B serology was negative in all. Hepatitis C serology was negative in one and not tested in the rest. Acute post-infectious glomerulonephritis needed to be excluded in these patients, as morphologic changes by LM can be similar to MPGN, and elevated ASO titers have been reported in patients with MPGN. Two patients complained of arthralgia, and in one of them (Case #8), leishmanial skin lesions were documented. Thus, secondary causes of MPGN such as lupus nephritis needed to be considered, and were excluded by negative serologic results and absence of tubuloreticular structures in all.

The association of hepatitis B and C and MPGN is well known.^{10,23-25} Hepatitis B serology was positive in only one patient. Although we were unable to evaluate the association of hepatitis C due to unavailability of results, a ten-fold higher incidence of hepatitis C was noted in Iranian MPGN patients in comparison to the normal population.²⁶

The pathogenesis of MPGN is poorly understood, and the question arises if different etiologic factors are responsible for the three subtypes of MPGN, or if genetic factors^{10,23-25,27,28} inherited complement components,^{29,30} or different individual immune responses determine the subtypes of MPGN. Type I MPGN is considered an immune complex glomerulonephritis. MPGN type II (dense deposit disease) is thought to be due to an inherited fundamental systemic disorder resulting in biochemical modification of the glycoproteins of normal basement membranes, with recurrence of dense deposits in the transplant.³¹⁻³³ In type III MPGN, "secondary" causes are suggested as etiologic factors, and it is also considered as a morphologic variant of type I MPGN.¹⁷ However, the real underlying etiology is unknown. The pathogenesis of type III MPGN is still disputed because of the morphologic differences, however, due to their similar clinical course, MPGN III and I are considered as variants of the same disease.

In this study, we observed that MPGN, especially type III, was one of the diseases with the highest incidence among Iranian patients. It was also noted that second biopsies showed decrease in cellularity, but increase in chronic tubulointerstitial and vascular changes.^{34,35}

Although the number of cases with two biopsies in this study was small (13 cases), steroids did not appear to improve the outcome in type I and III MPGN patients, as compared to patients who received antihypertensive and antiplatelet treatment without steroids.

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