Mesangiocapillary Glomerulonephritis

G. D'Amico1 and F. Ferrario

G. D'Amico, F. Ferrario, Division of Nephrology, San Carlo Borromeo Hospital, Milano, Italy
(J. Am. Soc. Nephrol. 1992; 2:S159–S166)

ABSTRACT
The clinical and histological features of idiopathic mesangiocapillary glomerulonephritis (MCGN) have been reviewed, with a survey of the most recent literature, including the retrospective analysis of the data of the Italian Study Group of Renal Immunopathology on 368 patients. In both major types of MCGN, six morphological variants have been characterized (classical MCGN, nodular MCGN, exudative MCGN, focal segmental MCGN, MCGN with massive deposits, and crescentic MCGN) that have different etiologic, pathogenetic, or clinical outcome correlates. Actuarial renal survival 10 yr after renal biopsy has been calculated with life-table analysis to be 60 to 65% in type I MCGN, without significant differences between treated and untreated patients; none of the therapeutic regimens tested up to now for this disease have been independently demonstrated to be efficacious. As for the pathogenesis, the interrelationships between the three mechanisms that contribute to the development of the morphological features of the disease (accumulation of electron-dense deposits on the subendothelial side of the glomerular basement membrane or within the glomerular basement membrane; mesangial proliferation and peripheral interposition; and infiltration of inflammatory cells, mainly monocytes) have been discussed, and the role of hypercomplementemia and circulating nephritogenic factors (NFA and NFI) has been analyzed. Available evidence suggests that MCGN is an immunocomplex-mediated disease, the deposition of immune deposits being the initiating phenomenon, whereas the morphologic changes and complement system activation are secondary events.

Key Words: Idiopathic glomerulonephritis, subendothelial deposits, hypercomplementemia, nephritogenic factors

1 Correspondence to Dr. G. D'Amico, Division of Nephrology, San Carlo Borromeo Hospital, Via Pio II, 3, 20153 Milano, Italy.
1046-6673/0210–S159$03.00/0
Journal of the American Society of Nephrology
Copyright © 1992 by the American Society of Nephrology

The term mesangiocapillary glomerulonephritis (MCGN), or alternatively membranoproliferative GN, has been proposed for the histopathologic entity characterized by: (1) Intense glomerular hypercellularity mainly due to mesangial proliferation involving both cells and matrix; (2) thickening of peripheral capillary walls by subendothelial immune deposits and/or intramembranous dense deposits of undefined origin; (3) mesangial interposition into the capillary wall, with splitting of the basement membrane (giving a "double contour" or "tramtrack" appearance by light microscopy) and new formation of the subendothelial basement membrane. We prefer to call this entity "mesangiocapillary GN," because this designation places emphasis on a basic diagnostic features of the disease, namely the dependence of peripheral capillary wall thickening on mesangial interposition.

This entity includes forms of unknown cause (idiopathic MCGN) and forms associated with systemic and infectious disorders (Table 1). Therefore, it designates a morphologic pattern that needs to be integrated within an etiologic context whenever possible.

MCGN is a rare disease, and its incidence seems to have decreased in the developed countries of the world over the past two decades (1,2). After a period of intensive study at the end of the 1960s and during the 1970s, the interest of investigators in this disease has suddenly faded, in spite of the many remaining questions.

We will comment on some of these unresolved questions, taking advantage of the experience of the Italian Study Group of Renal Immunopathology (ISGRIP), which has recently completed a retrospective analysis of the histologic and clinical features of 368 patients with idiopathic mesangio proliferative GN, mainly adults (3). One of us (F. Ferrario) acted as Coordinator of the Group and did the morphological review of the biopsy material for the entire population of patients.

HISTOLOGY
Two major and distinct categories of idiopathic MCGN have been identified, often referred to as type I and type II (4–7). In type I, there are glomerular subendothelial immune deposits and duplication of the peripheral glomerular basement membrane (GBM); in type II, dense homogeneous deposits of material occupy and expand the lamina densa of many renal basement membranes (glomerular, tubular, and arteriolar). A variant of type I MCGN,
TABLE 1. Classification of MCGN

<table>
<thead>
<tr>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Idiopathic MCGN</td>
</tr>
<tr>
<td>Secondary (Associated with Other Diseases):</td>
</tr>
<tr>
<td>Systemic immune complex disease</td>
</tr>
<tr>
<td>SLE</td>
</tr>
<tr>
<td>EMC type II cryoglobulinemia</td>
</tr>
<tr>
<td>Chronic Liver Diseases</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Infectious Diseases</td>
</tr>
<tr>
<td>Subacute endocarditis</td>
</tr>
<tr>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Infected ventriculoatrial shunt</td>
</tr>
<tr>
<td>Neoplasms</td>
</tr>
<tr>
<td>Leukemia and lymphoma</td>
</tr>
</tbody>
</table>

* Abbreviations: SLE, systemic lupus erythematosus; EMC, essential mixed cryoglobulinemia.

designated type III MCGN, has been described in the past few years. It differs mainly in the simultaneous presence of subendothelial and subepithelial deposits, associated with the lamination and disruption of the lamina densa of GBM (8–10).

In our opinion, the main classification must be restricted to types I and II to acknowledge the considerable ultrastructural and probable pathogenetic differences between them. "Variant 3" could be regarded as one end of a spectrum rather than as a separate type, because epimembranous deposits are found in both major types of MCGN (20% in the cases studied by ISGRIP) and their numbers may vary in repeat biopsies (11). The accurate analysis of the large amount of biopsy material by the investigators of the ISGRIP suggested that in both major types of MCGN there are at least six morphologic variants, with the following different etiologic, pathogenetic, or clinical outcome correlates.

"Classical" MCGN

"Classical" MCGN (Figure 1) demonstrates prevalent and massive mesangial proliferation and mesangial matrix expansion. This form should also include, as a subgroup, the "lobular" pattern characterized mainly by more marked mesangial expansion occluding the capillary lumina of some loops. (155 of 329 patients with type I MCGN studied by the ISGRIP were classified in this group.)

Nodular MCGN

Nodular MCGN is characterized by centrolobular sclerosis of the expanded mesangium (Figure 2) and is always associated with microaneurysmatic dilation of glomerular capillaries (Figure 3). This form, also presenting the disruption of anchoring points at

Figure 1. Classical pattern of MCGN. Massive mesangial proliferation and mesangial matrix expansion. Diffuse thickening of the capillary walls with double contour appearance. Trichrome, x250.

Figure 2. Nodular pattern of MCGN. Massive mesangial matrix expansion with diffuse centrolobular sclerosis. Periodic acid-Schiff, x250.

Figure 3. Nodular pattern of MCGN. Microaneurysmatic dilation of glomerular capillaries and concentric expansion of mesangial matrix with nodules formation. Silver stain, x400.
which peripheral capillary loop basement membranes attach to mesangial stalks, and probably due to a mesangiolytic process similar to that described in nodular diabetic nephropathy (12), was found in 60 of 329 cases of type I MCGN studied by the ISGRIP. Many of the features that characterize type I MCGN were present in these patients (e.g., mild mesangial proliferation and segmental peripheral interposition with thickening of the GBM, subendothelial deposits with the immunofluorescence (IF) pattern of "peripheral lobular" deposition of C3 and Immunoglobulin G (IgG), hypocomplementemia in one third of the cases), suggesting that it is a variant of such GN. However, the Italian investigators think that it should be distinguished from the "lobular" type I MCGN, because the morphogenetic mechanism of nodule formation with concentric enlargement of the mesangial matrix is strictly associated with microaneurysmatic dilations developing for unknown reasons (more severe mesangial damage with consequent mesangiolysis? more severe intracapillary hypertension? more severe vascular damage?). Moreover, in none of the 17 repeat biopsies from patients who had non-nodular variants of MCGN in the first biopsy could any transformation into the nodular pattern be identified, confirming that this variant of MCGN is not the late sclerotic stage of the classic variant, as the lobular pattern is.

Exudative MCGN

Although moderate infiltration of neutrophils and mononuclear inflammatory cells is often present in the classical form of type I MCGN, the infiltration of inflammatory cells, mainly monocytes, was massive in 13% of the patients studied by the ISGRIP, whereas mesangial proliferation and peripheral interposition was less marked than in the "classical" type I. Sub-epithelial deposits frequently coexisted with the sub-endothelial deposits, and the clearly visible "double contour" aspect of the thickened GBM was due to the subendothelial interposition of the infiltrating inflammatory cells rather than to mesangial interposition (Figure 4). This variant of proliferative-exudative GN, which closely resembles the morphologic pattern of the secondary forms of lupus proliferative GN, of cryoglobulinic GN, and of the GN associated with other infectious diseases (subacute bacterial endocarditis, shunt nephritis, schistosomiasis, malaria), is not classifiable "sensu stricto" as an MCGN, if we agree that mesangial proliferation and peripheral interposition, producing thickening and duplication of the basement membrane, are the hallmarks of this GN. The frequent associations with an acute nephritic syndrome, macroscopic hematuria, and marked hypocomplementemia at onset are also typical of acute proliferative GN. However, the chronic clinical course, with persistent hypocomplementemia, the immunohistologic features of diffuse subendothelial deposition of C3 (and often also IgG or IgM), and the persistence of mesangial activation in later stages, when infiltrating blood-borne cells are reduced in number, sharply differentiate this type of GN from the acute postinfectious GN, and characterize this morphological entity as a variant of MCGN.

Focal Segmental MCGN

In 13% of the patients in the ISGRIP study, the morphological features of the classical type I MCGN were present, but they were restricted to segments of the glomerular tuft. Some investigators tend to classify this GN as a distinct entity (13,14). However, repeat biopsies showing that focal segmental glomerular lesions could progress to diffuse MCGN and that, when diffuse MCGN improves, it may pass through the features of focal MCGN (15) suggest that segmental MCGN is a less aggressive disease or a stage of less marked damage during the natural course of the classical MCGN. The fact that the subendothelial deposition of C3 and IgG, seen by IF, is often diffused to all tufts within each glomerulus confirms this hypothesis.

GN With Massive Deposits

In a small number of the patients studied by the ISGRIP (4%), the thickening of the GBM was due to subendothelial massive deposits that could not be classified as amyloid, light chains, or cryoglobulins (Figure 5). The deposits seem, even by electron microscopy, to be amorphous (Figure 6). The mesangial proliferation is very mild, but the IF pattern and the persistent hypocomplementemia allow classification of this GN as a variant of MCGN. Further studies are necessary to characterize the composition of the material that accumulates in this GN.
Crescentic MCGN

In 2% of the patients with type I MCGN, coexisting either with the classical lobular pattern or the nodular pattern, circumferential crescents were found in more than 70% of glomeruli at the time of biopsy, which was performed because of a clinical syndrome of rapidly progressive deterioration of renal function. It is well known that such a severe pattern can be seen in all types of idiopathic or secondary GN. It is worth emphasizing that although the variants described above were selected from the large population of patients with type I MCGN, a similar spectrum of variants might also be found in patients with type II MCGN.

**PATHOGENESIS**

What is the interrelationship between the three mechanisms that seem to contribute to the development of the morphological features of MCGN: (1) accumulation on the subendothelial side of the GBM (type I) or within the GBM (type II) of electron-dense deposits that are probably immune complexes (ICx) in the first type and deposits of undefined origin in the second? (2) Mesangial proliferation involving both cells and matrix, with a tendency of the activated mesangium to expand to the peripheral capillary walls and to interpose in the subendothelial space, causing the specific splitting ("double contour" appearance) of the GBM? or (3) Inflow of blood-borne inflammatory cells, mainly monocytes?

The accumulated experience with experimental models of chronic immune complex-induced GN and with humans, in whom ICx deposit on the internal aspect of the GBM (chronic infectious diseases, systemic lupus erythematosus, type II EMC), suggests that deposits come first and are responsible for the other two mechanisms, a secondary activation of the mesangium that expands to the periphery of capillary walls with cytoplasmic extensions that engulf the deposits, as well as the inflow of leukocytes. However, these two mechanisms of defense are not necessarily activated to the same extent. When we look at the broad spectrum of lesions that can be associated with the prolonged deposition of ICx and complement in humans, we see that in some cases (lupus, cryoglobulinemic GN, the exudative variant of idiopathic MCGN), the prevailing mechanism of defense is the accumulation of monocytes and neutrophils in the subendothelial space; this is also responsible for the thickening and duplication of the GBM, with mesangial interposition being quite rare. At the other end of the spectrum, as in the classical type I idiopathic MCGN, there is little or no cell influx, and mesangial activation with peripheral interposition is the prevailing mechanism of defense.

It is possible that not only the amount, but also the nature and composition, of the subendothelial deposits accounts for the endothelial damage and the prevailing cytokine-mediated activation of mesangium or inflammatory cells, mainly monocytes. It is also possible that the recruitment of monocytes and polymorphonuclear cells is the prevailing mechanism when immune complexes are deposited acutely on the subendothelial aspect of the GBM, whereas mesangial activation and peripheral interposition are a later, more chronic phenomenon, favored by the cytokine-mediated stimulation of resident glomerular cells induced by the infiltrating monocytes. However, in some circumstances (cryoglobulinemic GN and some cases of idiopathic MCGN), monocyte infiltration can be demonstrated even in less-acute stages.
of the disease, in the absence of evident mesangial interposition.

When immunocomplexes are deposited on the internal side of the GBM, it can be postulated that mesangial interposition is a consequence of such deposition of complement and immunoglobulins. The regression of the mesangial expansion when exogenous bacterial antigens are eliminated from the body, as in shunt nephritis, confirms this hypothesis. However, it is more difficult to believe in it when the interposed mesangium contains no deposits or when such deposits stain only with complement, without accompanying immunoglobulins. It is possible that other mechanisms of injury of the capillary wall, especially if they induce endothelial damage and its detachment from the basement membrane, may also eventually stimulate the accumulation of plasma proteins and the ingrowth of the mesangium in the resulting subendothelial space, independent of the presence of deposits in such space (16).

A very characteristic feature, when the sequence of immunopathogenetic events described above (i.e., long-term accumulation of electron-dense deposits in the context or on the internal aspect of the GBM, recruitment of monocytes, and chronic mesangial activation with peripheral interposition) take place is the frequent coexistence of a protracted hypocomplementemia. In idiopathic MCGN, the association with low complement levels is so frequent that this GN has also been called "hypocomplementemic GN."

However, the cause of hypocomplementemia in idiopathic and secondary MCGN, its relationship to the pathogenesis, and its possible role in perpetuating the glomerular disease are still obscure. We also do not yet understand why in some cases (type II idiopathic MCGN) the activation of the alternative pathway is the prevailing phenomenon, whereas in other cases (type I idiopathic MCGN, lupus nephritis, cryoglobulinemic GN, shunt nephritis), there is activation of the classical pathway.

Similarly, it is unknown whether the hypocomplementemia is always a secondary phenomenon, derived from increased consumption triggered by subendothelial or intramembranous deposits, or it may precede such deposition and favor it. This latter hypothesis was proposed many years ago (17–19), because patients with MCGN have an increased incidence of inherited deficiencies of various complement components, and such deficiency could impair clearance of antigen-antibody complexes in response to viral or bacterial infections, leading to increased renal deposition and to the development of GN.

The rarity of such inherited deficiencies in MCGN, the fact that MCGN can occur and progress without concomitant hypocomplementemia, and the findings that low complement levels may normalize in patients with idiopathic hypocomplementemic MCGN after renal transplantation, only to accompany the recurrence of the disease in the transplanted kidney and that the GN can recur after transplantation even in some patients who had normal complement profiles before transplantation (20), suggest that the capillary wall changes come first and that hypocomplementemia is a consequence of the glomerular disease.

It has been recently demonstrated that the glomerulus of patients with idiopathic MCGN is a trigger of the alternative activation pathway in situ (21). However, there is no evidence that complement activation in situ in the glomerulus actually affects the serum levels of components of the system. Instead, it is now evident that hypocomplementemia can be ascribed to at least two circulating complement-reactive modalities: (1) the activation of the classical pathway produced by circulating immune complexes and (2) the presence in the blood of anticomplement autoantibodies, called "nephritogenic factors" (NF) (22–26). At least two nephritic factors have been described, one that acts on the amplification loop of the complement cascade (NFa) and the other that acts on the terminal pathway (NFt). The activation of the classical pathway by circulating immune complexes is probably the major mechanism responsible for hypocomplementemia in idiopathic type I MCGN, in lupus nephritis, and in shunt nephritis, whereas the effect of the circulating nephritogenic factor of the amplification loop (NFa) is probably the major mechanism responsible for the hypocomplementemia of type II idiopathic MCGN (22). However, nephritic factors are sometimes found in sera of patients of the former group (23). Even among patients with type I idiopathic MCGN, different circulating complement-reactive modalities may be set into operation and hypocomplementemia may be multifactorial in origin, the classical pathway being activated in some; in others, the presence of the nephritogenic factors NFt or NFa might better explain the abnormalities of the serum complement profile (23). In other words, different nephritogenic factors can be present in the same morphological type of MCGN, and the same nephritogenic factor can coexist in heterogeneous types of MCGN with quite different abnormalities of glomerular ultrastructure, such as type I and type II idiopathic MCGN.

To make things more complicated, neither circulating nephritogenic factors nor hypocomplementemia per se appears to be correlated with the clinical course of the different types of primary or secondary MCGN (27–29); therefore, they are not of value for monitoring the course or predicting the final outcome and, when persistently present, can only be considered markers of this group of glomerular diseases.

Obviously, even in idiopathic MCGN, as in most diseases of immunologic origin including a number
of glomerulonephritides, genetic predisposition has been investigated by looking at the major histocompatibility complex on the short arm of chromosome 6, which includes the genes coding for the determinants of the human leukocyte antigens A, B, C, and D regions, as well as the complement protein factors B, C2, C4A and C4B. It has been recently reported that the extended haplotype human leukocyte antigen B8, DR3, SC01, GLO2 is significantly more frequent in patients with type I MCGN than in normal controls (30) and that patients with this extended haplotype had a higher incidence of renal insufficiency than did those without it. These data are compatible with the presence of a gene on this extended haplotype that predisposes to type I MCGN. It is not yet known whether patients with type II MCGN have the same increased frequency.

NATURAL HISTORY AND TREATMENT

In recent years, studies of the long-term course of idiopathic MCGN have been carried out in a small number of patients because of the rarity of the disease. All of these studies indicated that the prognosis is generally unfavorable, but they did not clarify which factors may adversely influence the progression to end-stage renal failure.

In 1990, two multicenter studies, one from Germany (31) and the other from the ISGRIP (32), analyzed the long-term prognosis of sufficiently large populations of patients with type I MCGN: 220 patients in the German study, and 259 patients in the Italian one (Table 2). Both were mainly adult populations: only 5.5% of the German patients and 13.2% of the Italian patients were younger than 15 yr at the time of biopsy. The duration of follow-up was 59 months on average (median, 50 months) from the time of biopsy, 83 months (median, 60 months) from the apparent onset in the German study, and 60 (median, 42 months) and 78 months (median, 72 months) in the Italian study. At the end of this observation period, only 27 and 40% of patients maintained a normal renal function, whereas 22 and 5% had died; the calculated actuarial renal survival 10 yr after renal biopsy was 64% in the German and 60% in the Italian populations of patients with type I MCGN. The ISGRIP study also showed no difference in renal survival in comparison with 28 patients with type II MCGN similarly analyzed.

In both studies, the values of many clinical and histologic parameters as prognostic indicators were tested. Even though the choice of the parameters to evaluate and the statistical methods used for the univariate and multivariate analyses were not completely comparable, the results obtained were rather similar (Table 3). In the Italian study, but not in the German one, the severity of proteinuria appeared to be a bad prognostic sign. The importance of the interstitial damage (inflammatory infiltration and/or fibrosis) as a prognostic indicator deserves some comment. As already shown for membranous nephropathy (33), IgA nephropathy (34,35), and focal glomerulosclerosis (36), in MCGN (31), too, it can be hypothesized that the existence of a cell-mediated mechanism of interstitial damage, partly independent of the concomitant glomerular damage (even though possibly triggered by it), is probably responsible for the progression of the disease to end-stage renal failure (37,38). In the two studies, different criteria were adopted to classify the various subgroups of patients according to the extent and type of glomerular damage, and to evaluate the relative risk of renal death by the actuarial survival

<table>
<thead>
<tr>
<th>TABLE 2. Renal function at the end of follow-up in two retrospective multicenter studies in patients with idiopathic type I MCGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitt et al. (1990) (31)</td>
</tr>
<tr>
<td>No. of Patients</td>
</tr>
<tr>
<td>Patients with &lt;15 yr at Onset (%)</td>
</tr>
<tr>
<td>Mean Duration of Follow-Up (months)</td>
</tr>
<tr>
<td>From the time of biopsy</td>
</tr>
<tr>
<td>From apparent onset</td>
</tr>
<tr>
<td>Patients With Normal Renal Function (Δ) (%)</td>
</tr>
<tr>
<td>Patients With Impaired Renal Function (%)</td>
</tr>
<tr>
<td>Patients With End-Stage Renal Failure (RDT or Transplantation) (%)</td>
</tr>
<tr>
<td>Patients who Died (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 3. Clinical and histologic parameters that were associated with a less favorable outcome in two large cohorts of patients with idiopathic type I MCGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitt et al. (1990) (31)</td>
</tr>
<tr>
<td>Elevated Serum Creatinine</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Heavy Proteinuria</td>
</tr>
<tr>
<td>Glomerular Sclerosis</td>
</tr>
<tr>
<td>Interstitial Damage (Infiltration of Cells and Fibrosis)</td>
</tr>
<tr>
<td>Arteriolar Hyalinosis</td>
</tr>
</tbody>
</table>

* Δ Serum creatinine ≤1.3 in the German study, ≤1.5 in the Italian study.
curves of the Kaplan and Meyer methods. Therefore, the results of the analyses are difficult to compare. In the German study, renal survival was compared in five subgroups corresponding to five grades of increasingly severe glomerular changes. Only subgroup 5 with crescents was associated with a worse prognosis, in comparison with the other four subgroups, in which segmental, classical, and lobular variants were included (nodular pattern was not considered to be a separate subgroup). In the Italian study, both the crescentic and the nodular variants had a significantly worse prognosis than did the classical lobular variant, the focal segmental variant, the exudative variant, and the variant characterized by massive subendothelial deposits.

In both studies, actuarial renal survival was calculated separately for the subgroups of treated and untreated patients (52 versus 38% of patients in the Italian study; 57 versus 43% in the German study), including among the treated patients, all of those given anti-inflammatory (steroids or nonsteroidal anti-inflammatory drugs) and/or cytotoxic (cyclophosphamide or azathioprine) drugs for at least 2 months. No difference between treated and untreated patients could be found. Although, in the treated group, the different patients were given different types and combinations of drugs for variable periods of time, the results of this rough retrospective statistical analysis confirm the general impression that the above-listed classes of drugs do not have a demonstrable effect on the progression of idiopathic MCGN. The ISGRIP is now completing a multicenter randomized trial to confirm the efficacy of antiplatelet agents (ticlopidine is being tested), shown in 1984 by Donadio et al. (39) in a relatively small number of patients with the combination of dipyridamole plus aspirin.

REFERENCES


22. West CD: The complement profile in clinical


