Membranoproliferative Glomerulonephritis
Common Glomerular Disease - Changing Pattern of Biopsy Proven Renal Disease in a Tertiary Care Hospital

S Himamani
Associate Professor and Head, Department of Nephrology, Mysore Medical College and Research Institute, Mysore, Karnataka, India

Abstract

Introduction: Glomerular diseases are common causes of all renal syndromes including acute renal failure, chronic renal failure, and end-stage renal diseases, and thus they lead to increased morbidity and mortality worldwide. Hence making a definitive diagnosis in the initial stages of these glomerular disease helps in better management. Among glomerular diseases, there is a changing trend in the incidence worldwide and within India.

Materials and Methods: This is a retrospective analysis of kidney biopsies over a period of 1-year 3-month, from September 2014 to December 2015. A total of 60 kidney biopsies were included in the analysis.

Results: The most common indication of kidney biopsy was a nephritic syndrome. The most common histopathology was membranoproliferative glomerulonephritis (MPGN) which was seen in 21 biopsies that is the incidence of 35% among all kidney biopsy. Among the glomerular disease, MPGN was seen in 41%, the increased numbers can be due to varied etiologies including primary and secondary causes. Secondary causes include infections, connective tissue diseases, malignancies, hereditary and acquired complement factor and complement regulatory factor defects.

Conclusion: MPGN was commonest biopsy proven nephropathies in our study in contrast to other studies which have revealed it to be less. Study as concluded that immune complex mediated MPGN is common in study population which included adults.

Key words: Acute nephritic syndrome, Acute renal failure, Acute tubular necrosis, Chronic glomerulonephritis, C3 glomerulonephritis, Focal proliferative glomerular disease, Immunoglobulin A nephropathy, Lupus nephritis, Membranoproliferative glomerulonephritis, Membraneous nephropathy, Minimal change disease, Multiple myeloma, Nephrotic syndrome, Post-infectious glomerulonephritis, Rapidly progressive renal failure, and Rapidly progressive glomerulonephritis

INTRODUCTION

Membranoproliferative glomerulonephritis (MPGN) is third to fourth leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide. Its presentation include from benign and slowly progressive to rapidly progressive glomerular disease, it includes microscopic hematuria and non-nephrotic proteinuria (35%), nephrotic syndrome (NS) (35%), chronically progressive GN (20%), and rapidly progressive glomerulonephritis (RPGN) (10%). We have analyzed the clinical presentations, clinical syndromes, clinicopathological correlation, and prognosis in these subjects and this analysis is very important since MPGN is one of the common cause of ESRD all over the world and the recurrence rate is very high following renal transplantation, especially for Type 11 MPGN. Hence, early renal biopsy, and optimal treatment would decrease the burden of ESRD in these subjects. MPGN is traditionally classified into three subtypes on the basis of pathological features identified by light, immune fluorescence, and
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1 (33.3) 1 (33.3) 1:0 (100/0%) 16 (89) 3 (16.6) 9 (50) 2 (66.6) 6 (33.3) 4 (22) 41±6.4 3 (16.6) 0 (0) 1 (33.3) 1:1.5 (38/62%) 0 (0)

MATERIALS AND METHODS

Kidney biopsies performed in our institute from September 2014 to December 2015 were retrospectively analyzed.

Inclusion Criteria

All adult patients with an indication to do a renal biopsy.

Exclusion Criteria

Biopsies of the native kidney with other diagnosis other than MPGN, transplant kidney, tumor, and inconclusive results.

Details for each patient: Name, age, sex, indication for renal biopsy, histopathological diagnosis, various type of MPGN like immunoglobulin or complemented mediated, primary or secondary form of MPGN and laboratory investigations such as serum creatinine, 24-h urinary protein, urine microscopy, virology (hepatitis B surface antigen [HBsAg], anti-hepatitis C virus [HCV], HIV), and serology (anti-dsDNA antibody, antinuclear antibody), C3, C4 were recorded. Renal biopsy specimens were analyzed by pathologist. Analysis included light microscopy and immunofluorescence (IF). EM was done whenever it was indicated. Indications for renal biopsy were: NS, acute nephritic syndrome, asymptomatic urinary abnormalities, hematuria, non-recovering acute renal failure (ARF), chronic renal failure (if biopsy was feasible), and rapidly progressive renal failure, RPGN. Automated biopsy guns were used to do biopsy. Data were analyzed and compared with studies published from India and different regions of the world.

Statistical Analysis

Simple descriptive statistics such as median and mean ± standard deviation were used for variables such as age, clinical, and laboratory features. Percentage was used for categorical data.

RESULTS

Among all renal pathologies in 60 patients primary glomerulonephritis (PGN) is the most predominant renal disease as analyzed in our study, followed by secondary glomerulonephritis (SGN) and tubulointerstitial nephritis. The vascular diseases are less frequent. MPGN was the common manifestation of both PGN and SGN.

Of the 21 patients with MPGN, 18 (86%) patients had immune complex associated MPGN, and 3 (14%) had complement associated MPGN. 15 (71%) patients had primary MPGN, and 6 (25%) had secondary MPGN. Mean age (years) at presentation was 41 ± 6.4 for immune complex associated MPGN and 32 ± 5.6 for complement associated MPGN. Since our center does not include pediatric patients we did not have pediatric patients. Male to female ratio in an immune complex associated MPGN was 1:1.5 and for complement associated MPGN it was 1:0. Of 21 cases 6 patients had secondary MPGN, three had lupus nephritis (LN), one had multiple myeloma (MM), one had HBsAg positive and one patient had chronic osteomyelitis (Table 1).

The most common clinical syndrome was a nephritic syndrome, in an immune complex associated MPGN it was 50% and in complement associated MPGN it was 33.3% similarly in this category ARF, CKD were also equally seen. However, in an immune complex associated MPGN ARF incidence was 16.6%, CKD incidence was 16.6%, NS was 33.3%, and RPGN 22%. Hypertension was very common in these patients it was seen in 89% of immune complex associated MPGN and 66.6% in complement associated MPGN. All patients who presented with RPGN had crescentic glomerulonephritis. All patients with CKD had significant glomerular sclerosis and interstitial fibrosis and tubular atrophy. Other than CKD only 2 patients had interstitial fibrosis and tubular atrophy of 5-10% only (Table 2).

Most common histopathology finding was hypercellularity and lobularity of the glomeruli (85%), followed by a double contoured basement membrane (73%). Based on immunofluorescence MPGN are classified, immune complex associated MPGN (86%)

| Table 1: Clinical characteristics of the patients at presentation according to MPGN type |
|---------------------------------|----------------|----------------|
| Characteristics                     | Immune complex associated MPGN | Complement associated MPGN |
| Age (years) (mean)                  | 41±6.4                  | 32±5.6                  |
| Male/female (ratio) (%)             | 1:1.5 (38/62%)          | 1:0 (100/0%)            |
| Hypertension n (%)                  | 16 (89)                 | 2 (66.6)                |
| Nephritic n (%)                     | 9 (50)                  | 1 (33.3)                |
| Nephrotic n (%)                     | 6 (33.3)                | 0 (0)                   |
| ARF n (%)                           | 3 (16.6)                | 1 (33.3)                |
| CKD n (%)                           | 3 (16.6)                | 1 (33.3)                |
| RPGN n (%)                          | 4 (22)                  | 0 (0)                   |

MPGN: Membranoproliferative glomerulonephritis, ARF: Acute renal failure, CKD: Chronic kidney disease, RPGN: Rapidly progressive glomerulonephritis
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and complement associated MPGN (14%). 100% biopsy specimen had C3 positivity; that is C3 deposit in glomeruli capillary and mesangium was the most common deposit. Immunoglobulin G (IgG) was positive in 85%, IgM was positive in 76%, C1q deposits in 60%, least common deposits were IgA in 18%.

Though it is seen that full house pattern (IgG, IgM, IgA, C3, C1q) is common in LN, in our study, it is seen in 100% of LN but two primary MPGN cases also had full house pattern.

Figure 1 shows the histopathology in MPGN, hematoxylin and eosin stain showing hypercellular and lobulated glomeruli with fibrocellular crescent, atrophied tubules are also seen.

After definitive diagnosis by renal biopsy, treatment was started. Among 15 primary MPGN, 4 CKD patients were not on any immunosuppresion, three of these CKD patients are not on dialysis and one is dialysis dependent. In remaining 11 patients, crescentric glomerulonephritis patients were started treatment with cyclophosphamide followed by steroids. All other cases are on treatment with steroids and mycophenolate. Among secondary causes of MPGN, MM case referred to an oncologist for further management. Chronic osteomyelitis with MPGN case is dialysis dependent, HBsAg case is on antiviral and steroids, among the LN cases one patient died, and other two are on immunosuppresion treatment.

**DISCUSSION**

MPGN is also called mesangicapillary GN. MPGN may be idiopathic or secondary. Secondary causes include: (1) Immune complex mediated, and (2) complement-mediated causes.

1. Immune complex associated condition include:
   a. Infection
   b. Autoimmune or rheumatological diseases
   c. Malignancy.
      - Infections: HCV (70-90% of patients), bacterial endocarditis, chronic hepatitis B viral infection, abscess, infected ventriculoatrial shunt, human immunodeficiency virus; hantavirus malarial (*Plasmodium malariae*), schistosomal infections, chronic fungal infection can cause MPGN
      - Collagen vascular disease: Systemic lupus erythematosus, Sjögren’s syndrome
      - Malignancy: Chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, light chain deposition diseases like MM.

2. Complement-mediated MPGN includes hereditary complement deficiency (C1q, C2, C4, or C3), acquired complement deficiency (presence of C4 nephritic factor), associated with factor H defect or autoantibodies to factor H. This type MPGN can be associated with or without partial lipodystrophy and retinal abnormalities.

In immune-complex-mediated MPGN. Deposition of immune complexes in the glomeruli occurs due to persistent antigenemia. This leads to antigen-antibody immune complexes formation. Elevated levels of circulating immune complexes occur in chronic infections, autoimmune diseases, and paraproteinemias due to monoclonal gammopathies. These immune complexes trigger the activation of the classical pathway of complement and cause deposition of complement factors of the classical pathway and terminal complement pathway in the mesangium and along the capillary walls. A kidney biopsy specimen typically shows both immunoglobulin and complement on IF microscopy.

Complement-mediated MPGN. The complement cascade plays an important role in innate immunity. Complement
factors can induce a potent inflammatory response that results in phagocyte chemotaxis, with opsonization and lysis of cells, including microorganisms. Complement activation occurs through the classical, lectin, or alternative pathways, all of which converge to form C3 convertase, which cleaves C3 into C3a and C3b. C3b, in the presence of factor B and factor D, associates with C3 convertase, generating even more C3 convertase and results in a potent amplification of the inflammatory loop. Thus, C3 convertase is a nodal point in the complement cascade. The association of C3b and C3 convertase also results in the formation of C5 convertase, which activates the terminal complement complex pathway and the formation of the membrane attack complex (C5b-C9) on cell surfaces, thereby resulting in lysis including damage to cell membranes such as the glomerular basement membrane as well as membranes of pathogenic microorganisms. To prevent self-damage, activation of the alternative pathway occurs in a tightly regulated, sequential manner. Multiple complement-regulating and complement-inhibiting proteins operate at different levels of the cascade, particularly at the C3 and C5 convertase level. Such regulators include factors H and I and factor B, decay-accelerating, factor (CD55), membrane cofactor protein. Hence, either defect in these complement regulator proteins or autoantibodies to these regulatory proteins causes unregulated complement activation and damage to glomeruli.\(^6\)

In our study the most common type of MPGN was immune complex mediated. Hence, the incidence of the complement mediated condition is rare, only three out of 21 case had this type of MPGN. This may be due to the study population in our study include only adults and complement-mediated MPGN are common in children and adolescents. We can conclude that inherited defect, mutations and autoantibodies to complement regulatory proteins are rare in the adult population. In contrast, to this entity the overall MPGN was very high in contrast to most studies which reveal it to be 7-10\(^\%\).\(^1,2\) In our study, it is 35\(^\%\). Compared to complement-mediated MPGN immune complex MPGN was the predominant category, 85\(^\%\) of the MPGN in the study population. Again the secondary causes were seen in only 6 out of 21 patients, three cases of LN, one case of MM, one case associated with chronic osteomyelitis and one case with HBsAg positive.

Hence, there is an increased number of idiopathic MPGN. The high incidence in our study may be our institute is a tertiary care hospital which provides medical service to low socioeconomic class of people. These patients are prone for persistent subclinical and chronic infections which may lead to chronic antigenemia and immune complex activation and predispose them to develop MPGN. This emphasize that overall control and prevention of infection at this level of low socioeconomic class of people would decrease the incidence of MPGN in these people.

The main drawback of the study is it included a small group of people since it as analyzed over a period of 1-year 3-month, more longer duration of the study with more number of study group would give a better understanding of these cases of MPGN.

**CONCLUSION**

The study has highlighted the changing trend in the glomerular disease, MPGN being the most common disease. Since it appears to be related to chronic subclinical infection, most of these can be decreased by prevention of infection.

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**REFERENCES**