

Clinical and histological features of patients with membranoproliferative glomerulonephritis classified by immunofluorescence findings

Características clínicas e histológicas de pacientes com glomerulonefrite membranoproliferativa classificados por achados de imunofluorescência

Authors

Cristiane Bitencourt Dias ¹
Leonardo Testagrossa ²
Lectícia Jorge ¹
Denise Malheiros ²
Viktoria Woronik ¹

¹ Universidade de São Paulo, Escola de Medicina, Hospital das Clínicas, Departamento de Nefrologia, São Paulo - SP, Brazil.

² Universidade de São Paulo, Escola de Medicina, Hospital das Clínicas, Departamento de Patologia, São Paulo - SP, Brazil.

ABSTRACT

Background: New classification for membranoproliferative glomerulonephritis has been proposed in the literature. The aim of this study was to compare the clinical, biochemical, etiology and renal biopsy findings of these patients grouped by immunofluorescence as proposed by the new classification. **Methods:** Patients with renal biopsy-proven membranoproliferative glomerulonephritis unrelated to systemic lupus erythematosus, diagnosed between 1999 and 2014. The patients were divided according to immunofluorescence: Immunoglobulin positive group, C3 positive only and negative immunofluorescence group. **Results:** We evaluated 92 patients, the majority of which were in the immunoglobulin positive group. Infectious diseases, hepatitis C virus and schistosomiasis, were the most frequent etiology. A negative immunofluorescence group had more vascular involvement in renal biopsy compare with others groups. **Conclusions:** The only difference between the groups was higher vascular involvement in renal biopsy in negative immunofluorescence group. These new classification was satisfactory for the finding of etiology in one part of the cases.

Keywords: complement system proteins; epidemiology; glomerulonephritis, membranoproliferative; microscopy, fluorescence.

RESUMO

Introdução: Uma nova classificação para glomerulonefrite membranoproliferativa foi proposta na literatura. O objetivo deste estudo foi comparar os achados clínicos, bioquímicos, etiológicos e da biópsia renal desses pacientes agrupados por imunofluorescência, conforme proposto pela nova classificação. **Métodos:** Pacientes com glomerulonefrite membranoproliferativa comprovada por biópsia renal, não relacionada ao lúpus eritematoso sistêmico, diagnosticados entre 1999 e 2014. Os pacientes foram divididos de acordo com a imunofluorescência: grupo positivo por imunoglobulina, grupo positivo por C3 apenas e grupo com imunofluorescência negativa. **Resultados:** avaliamos 92 pacientes, a maioria dos quais estava no grupo de imunoglobulina positiva. Doenças infecciosas, o vírus da hepatite C e a esquistossomose, foram as etiologias mais frequentes. Um grupo com imunofluorescência negativa apresentou maior comprometimento vascular na biópsia renal quando comparado com os outros grupos. **Conclusões:** a única diferença entre os grupos foi o maior envolvimento vascular na biópsia renal no grupo de imunofluorescência negativa. Esta nova classificação foi satisfatória para a descoberta de etiologia em uma parte dos casos.

Palavras-chave: epidemiologia; glomerulonefrite, membranoproliferativa; palavra; microscopia, fluorescência; proteínas do sistema complementar.

INTRODUCTION

Membranoproliferative glomerulonephritis (MPGN) diagnosis occurred in 79 (4.2%) patients out of 1849 with glomerulonephritis enrolled in Paulista Registry of Glomerulopathies from 1999 to 2005.¹ This glomerulopathy is more often associated with secondary causes, especially infection

by hepatitis C virus (HCV) and autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.² However Little *et al.*³ identified 34% of idiopathic forms in a group of predominantly male patients aged 24.9 years with nephrotic syndrome and low levels of complement C3 fraction in half of them.

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Correspondence to:
Cristiane Bitencourt Dias.
E-mail: cristianebitencourt@uol.com.br

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Histologically, MPGN is characterized by mesangial proliferation, matrix expansion and its interposition between the endothelium and the glomerular basement membrane, giving the capillary loops a double-contour appearance. In classical studies MPGN was categorized in three types, according to the location of the electron-dense deposit on electron microscopy: type I (subendothelial deposits); type II (dense homogeneous intramembranous deposits); type III (a variant of type I, with subepithelial and subendothelial deposits). Type I was associated with HCV infection, whereas type II affects younger individuals and was not related to systemic causes.⁴

Sethi and Fervenza⁵ proposed a new system of classifying MPGN based on immunofluorescence (IF), defining two groups: MPGN with immunoglobulin deposition on IF that could be associated to autoimmune diseases, infections, or monoclonal gammopathy, whereas MPGN without immunoglobulin deposition but with C3 deposition on IF that is classified as dense deposit disease (DDD) or C3 glomerulonephritis after electron microscopy examination. In other study, MPGN with none deposition seen on IF was introduced with other group and could be secondary to membrane reactions, as in thrombotic microangiopathy.⁶ In this new classification the use of electron microscopy is mandatory in cases of exclusive C3 deposition, in order to differentiate DDD and C3 glomerulonephritis.⁵

The new classification proposed by Sethi and Fervenza⁵ emphasizes the various mechanisms involved in the pathogenesis of MPGN, drawing distinctions between MPGN mediated by immune complexes, which had immunoglobulin deposition, and MPGN resulting from abnormalities of the alternative complement pathway with C3 deposition only. Some authors believe that idiopathic forms should be very rare emphasizing complement and genetic studies in these patients in order to clear their diagnosis.⁷

C3 glomerulopathy defined after Sethi and Fervenza⁵ as a MPGN with exclusive C3 deposition allows pathological discussion. Pickering *et al.*⁸ proposed a less restrictive definition with deposition of dominant C3 at least two orders of magnitude more intense than any immunoglobulin. In doing so most cases of immune complex diseases would be excluded.

Because of recent proposed classification, we aimed to conduct a retrospective single center study of MPGN patients grouped by the new IF-based

classification to compare clinical and biochemical characteristics, renal biopsy dates and follow up of patients, as well as the etiology in each group.

METHODS

STUDY DESIGN

This was a retrospective study of patients diagnosed by renal histology with MPGN between 1999 and 2014 in the Nephrology Department of the *Hospital das Clínicas* of the School of Medicine of University of São Paulo, in São Paulo Brazil. Clinical and biochemical characteristics were retrieved from clinical charts on admission and during follow-up.

Patients with SLE based on classical criteria^{9,10} were excluded, as were those for whom there were insufficient data from the renal biopsy or on the patient chart at diagnosis.

BIOCHEMICAL AND CLINICAL CHARACTERISTICS

At diagnosis were analyzed the following parameters: 24-h proteinuria, measured by the automated colorimetric method; urinalysis; serum creatinine, measured by the kinetic colorimetric method; glomerular filtration rate (GFR), calculated by the Modification of Diet in Renal Disease equation;¹¹ C3 and C4 complement fractions, measured by immunoturbidimetry, with reference ranges of 90-180 mg/dL and 10-40 mg/dL, respectively; serology for hepatitis B virus (HBV), HCV, and HIV; antinuclear factor; rheumatoid factor, serum proteins, measured by immunofixation. We assessed those same parameters at the end of follow-up, defined as the last visit to the facility.

Hematuria was defined > 10 red blood cells per field in two first morning urine specimens. Hypertension was defined as arterial blood pressure > 140/90 mmHg in two measurements on different days¹² or previous use of antihypertensive drugs, regardless of blood pressure levels.

RENAL BIOPSY

All patients included had been diagnosed with MPGN on light microscopy. The patients were divided into three groups according to the result of the immunofluorescence assay: with dominant immunoglobulins and eventually presence of complements (immunoglobulin positive group); with C3 deposition-only and no immunoglobulins (C3 positive group); negative IF (IF negative group). Positivity for immunoglobulin

deposition was defined as a score of 1+ or more for any type of immunoglobulin.

The so-called “full-house” immunofluorescence pattern was defined as concomitant deposition of three immunoglobulins and two complements. In the tubulointerstitial compartment, we assessed fibrosis or atrophy, categorized by the proportional involvement of the sample: $\geq 50\%$; $\leq 10\%$; or 11-49%. Vascular compartment was evaluated by the presence of any kind of involvement.

STATISTICAL ANALYSIS AND ETHICAL STATEMENTS

Continuous variables were expressed as mean \pm standard deviation for samples with normal distribution or as median and interquartile range for those without, whereas categorical variables were expressed as absolute and relative frequencies. Differences between the three groups for continuous variables were determined by analysis of variance or by the Kruskal-Wallis test, as appropriate. For the analysis of categorical variables, we used the chi-square test. Correlations were obtained by Pearson's or Spearman's correlation analysis, as appropriate. Values of $p < 0.05$ were considered statistically significant and all analysis was performed in Prism version 5.0 software.

The study was based exclusively on obtaining the records of patients' data, so we consider the approval of the Nephrology department as sufficient for its realization.

RESULTS

After excluding patients with lupus nephritis, we obtained a sample of 100 patients resting 92 for baseline analysis after exclusion of 3 patients lacking biochemical data and 5 lacking IF analysis. Therefore, the final sample comprised 92 patients aged 44.3 ± 15.4 years, 62% male and 38% female. Other characteristics at diagnosis are shown in Table 1. Of note are hematuria in 71.7% of cases, hypertension in 55.4%, mean proteinuria of 6.2 ± 3.4 g/day, mean serum albumin of 2.5 ± 0.6 mg/dL, median GFR of 41.5 mL/min/1.73 m², and serum creatinine of 1.8 mg/dL. After computing missed data C3 levels in 7 patients and C4 in 6 patients, low levels of C3 were present in 47.8% and for C4 in 31.5%.

ANALYSIS OF GROUPS BY IMMUNOFLUORESCENCE FINDINGS

Using the new, IF-based MPGN classification system, we found that 73 patients (79.3%) were in the

TABLE 1 CLINICAL AND BIOCHEMICAL DATA ON DIAGNOSIS IN PATIENTS WITH MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Characteristic	N = 92
Age (years)	44.3 \pm 15.4
Male gender, <i>n</i> (%)	57 (62.0)
Creatinine (mg/dL)	1.8 (1.3-3.5)
GFR (mL/min/1.73m ²)	41.5 (20.0-58.7)
Proteinuria (g/day)	6.2 \pm 3.2
Serum albumin (g/dL)	2.5 \pm 0.6
Low C3, <i>n</i> (%)	44 (47.8)
Low C4, <i>n</i> (%)	29 (31.5)
Low C3 and C4, <i>n</i> (%)	25 (27.1)
Arterial hypertension, <i>n</i> (%)	51 (55.4)
Hematuria, <i>n</i> (%)	66 (71.7)

The values for continuous variables are expressed as the mean \pm SD, or as the median (interquartile range).

GFR, glomerular filtration rate (as estimated with the Modification of Diet in Renal Disease equation).

immunoglobulin positive group, 9 (9.7%) were in the C3 positive group, and 10 (10.8%) were in the IF negative group. Clinical and biochemical data collected at diagnosis showed no differences among the three groups for any of the clinical or biochemical parameters evaluated (Table 2).

All groups at diagnosis showed low GFR (immunoglobulin positive 41.0 (20.0-65.0) mL/min/1.73m² vs. C3 positive 42.0 (15.5-50.0) mL/min/1.73m² vs. IF negative 39.5 (11.2-53.5) mL/min/1.73m², $p = 0.84$) and nephrotic proteinuria (immunoglobulin positive 6.3 ± 3.4 g/day vs. C3 positive 6.0 ± 3.0 g/day vs. IF negative 5.5 ± 3.5 g/day, 0.91). Immunoglobulin positive group had more patients with hypertension but with no statistical difference between the other groups and the IF negative group had 100% of cases with hematuria (Table 2). Immunoglobulin positive group showed missed data for C3 levels in 6 patients and for C4 in 6 patients while only one patient in the IF negative group showed missed C3 data.

Table 3 shows associations of MPGN and systemic diseases. Infectious diseases predominate in the three groups with 22 patients in Immunoglobulin positive, 3 in C3 positive and 3 in IF negative.

In the immunoglobulin positive group, we found a clinical association with HCV infection ($n = 7$), schistosomiasis ($n = 6$), HIV ($n = 2$), combination of HCV and HIV ($n = 2$), combination of HBV and HCV ($n = 1$), HBV ($n = 1$), syphilis ($n = 1$), endocarditis ($n = 1$), and leprosy ($n = 1$). Autoimmune disease was

TABLE 2 CLINICAL AND BIOCHEMICAL PARAMETERS IN THE THREE GROUPS ON DIAGNOSIS

Parameter	Immunoglobulin positive (n = 73)	C3 positive (n = 9)	IF negative (n = 10)	p-value
Age (years)	44.9 ± 14.6	44.6 ± 20.0	43.8 ± 15.0	0.44
Male gender, n (%)	45 (61.6)	6 (66.6)	7 (70.0)	0.57
Creatinine (mg/dL)	1.8 (1.1-3.6)	1.8 (1.3-5.4)	2.1 (1.6-5.1)	0.45
GFR (mL/min/1.73m ²)	41.0 (20.0-65.0)	42.0 (15.5-50.0)	39.5 (11.2-53.5)	0.84
Proteinuria (g/day)	6.3 ± 3.4	6.0 ± 3.0	5.5 ± 3.5	0.91
Serum albumin (g/dL)	2.5 ± 0.6	2.5 ± 0.3	2.7 ± 0.5	0.22
Low C3, n (%)	35 (52.2)	4 (44.4)	5 (50.0)	0.63
Low C4, n (%)	23 (34.3)	2 (22.2)	4 (40.0)	0.70
Low C3 and C4, n (%)	18 (26.8)	2 (22.2)	3 (30.0)	0.91
Arterial hypertension, n (%)	41 (56.0)	2 (22.2)	3 (30.0)	0.06
Hematuria, n (%)	51 (70.0)	5 (55.5)	10 (100.0)	0.07

The values for continuous variables are expressed as the mean ± SD, or as the median (interquartile range).

ns, not significant; GFR, glomerular filtration rate (as estimated with the Modification of Diet in Renal Disease equation).

TABLE 3 SYSTEMIC DISEASES ASSOCIATED WITH MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS ON DIAGNOSIS

Disease	Immunoglobulin positive (n = 73)	C3 positive (n = 9)	IF negative (n = 10)	p-value
Infection, n (%)	22 (30.1)	3 (33.3)	3 (30.0)	0.98
Autoimmune disorder, n (%)	8 (11.0)	0 (0.0)	1 (10.0)	0.57
Dysproteinemia, n (%)	3 (4.1)	1 (11.1)	2 (20.0)	0.14
Other, n (%)	4 (5.5)	1 (11.1)	0 (0.0)	0.56
None, n (%)	36 (49.3)	4 (44.4)	4 (40.0)	0.83

present in 8 patients of the immunoglobulin positive group: autoimmune hepatitis (n = 1), Takayasu arteritis (n = 1), antiphospholipid syndrome (n = 1) and “lupus like nephritis” defined as MPGN pattern with “full-house” deposits not meeting criteria for lupus was found in 5 patients. Monoclonal gammopathy or dysproteinemia was found in 3 patients of immunoglobulin positive group: lymphoma (n = 1), chronic lymphocytic leukemia (n = 1) and myeloma (n = 1). Furthermore, in 4 patients, there were associations with diseases rarely reported in MPGN: melanoma (n = 1), spherocytosis (n = 1) and alcoholic cirrhosis (n = 2).

In the C3 positive group, there was an association with HCV in 2 patients, HBV in 1, lymphoma in 1, and alcoholic cirrhosis in 1. Among the patients in the IF negative group, there was association with HCV in 2 patients, schistosomiasis in 1, essential cryoglobulinemia in 1, myeloma in 1, and Castleman’s syndrome in 1.

The most common associated disease in MPGN patients was HCV infection observed in 14 (15.2%) patients. Excluding those co-infected with HBV (n = 1) and HIV (n = 2), 11 patients with mono infection with HCV were analyzed. Their mean age was 45.8 ± 10.9 years, 63.6% had hypertension, males predominate (63.6%), mean proteinuria was 5.9 ± 2.5 g/day, mean serum albumin was 2.7 ± 0.6 g/dL, median serum creatinine was 2.3 mg/dL (1.1-8.0 mg/dL), and mean GFR was 33 mL/min/1.73 m² (6-71 mL/min/1.73 m²). In addition, 81.8% had hematuria, 54.5% had cryoglobulinemia and 80.0% of those tested for C3 and C4 (10 patients) showed low levels of C3 or C4.

Histological analysis showed 2 patients with crescents, 3 with vascular involvement, and 2 with interstitial fibrosis involving > 50% of the biopsy sample. Seven of the 11 patients were classified in the immunoglobulin positive group and showed IgM as the predominant immunoglobulin, 2 patients were in

the C3 positive group, and 2 were in the IF negative group. After a mean follow-up of 81.6 months, 2 patients had progressed to dialysis.

RENAL HISTOLOGY

Crescents were observed in 24.6%, 33.3%, and 30.0% of the patients in the immunoglobulin positive, C3 positive, and IF negative groups, respectively, without statistical difference between them (Table 4). The vast majority showed crescents in less than 10% of the glomeruli, except for two patients, one with HCV who showed crescents in 18% and another with idiopathic MPGN who showed crescents in 44%.

SCLEROTIC GLOMERULI

Sclerotic glomeruli were found in 9.5%, 11.1%, and 10.0% of the patients in the immunoglobulin positive, C3 positive and IF negative groups, respectively, without statistical difference between them (Table 4).

TUBULOINTERSTITIAL INVOLVEMENT

The vast majority of patients showed some tubular atrophy and interstitial fibrosis, which was observed in 65.7%, 88.8%, and 80.0% of the patients in the immunoglobulin positive, C3 positive, and IF negative groups, respectively, without statistical difference between them (Table 4). The proportion of patients showing severe (> 50%) impairment was similar in all three groups: 7.6%, 12.5%, and 10.0%, respectively.

VASCULAR INVOLVEMENT

The only findings of vascular involvement were intimal fibrosis and hyalinization of the arteriolar wall and they were observed in 37.0%, 33.3%, and 80.0% of the patients in the immunoglobulin positive, C3

positive and IF negative groups, respectively, showing a statistical difference ($p = 0.03$) corresponding to more vascular involvement in IF negative group (Table 4).

IMMUNOFLUORESCENCE FINDINGS

Table 5 describes the immunofluorescence findings in the immunoglobulin positive group. IgG was present in 43 patients and was the only immunoglobulin in 6, associated with IgM in 18, associated with IgA in 4, associated with IgM and IgA in 3 and associated with C3 in 12 patients. In 3 patients there was deposition of IgM alone while in 19 IgM deposited with C3 and in one patient IgM deposited with IgA. In 2 patients the only immunoglobulin deposited was IgA together with C3 deposition. The “full-house” pattern was observed in 5 patients.

FOLLOW-UP

Twenty four patients from immunoglobulin positive group were lost to follow-up. Among the remaining 49 patients, mean follow-up period was 76.7 ± 52.0 months and 14 patients (28.5%) progressed requiring renal replacement therapy while 35 patients ended with mean serum creatinine of 1.5 ± 1.1 mg/dL.

In the C3 positive group, 4 patients were lost to follow-up and the remaining 5 patients had been followed for an average of 29.2 ± 30.8 months. Four (80%) of those 5 patients required renal replacement therapy, and the remaining patient ended with serum creatinine level of 1.5 mg/dL.

Only one patient from 10 of IF negative group was lost to follow-up. The mean follow-up time of the group was 53.4 ± 45.5 months and 4 patients (44.4%) progressed requiring renal replacement therapy while the mean final serum creatinine level among the remaining 5 patients was 1.6 ± 0.9 mg/dL.

TABLE 4 LIGHT MICROSCOPY FINDINGS

Finding	Immunoglobulin positive (n = 73)	C3 positive (n = 9)	IF negative (n = 10)	p-value
Crescents, n (%)	17 (24.6)	3 (33.3)	3 (30.0)	0.74
Sclerotic glomeruli, n (%)	7 (9.5)	1 (11.1)	1 (10.0)	0.98
Tubular atrophy/ interstitial fibrosis, n (%)	48 (65.7)	8 (88.8)	8 (80.0)	0.27
Vascular involvement, n (%)	27 (37.0)	3 (33.3)	8 (80.0)	0.03

TABLE 5 IMMUNOGLOBULIN AND COMPLEMENT DEPOSITION IN IMMUNOGLOBULIN POSITIVE GROUP

Deposition	n = 73
IgG, n (%)	6 (8.2)
IgG + IgM, n (%)	18 (24.7)
IgG + IgA, n (%)	4 (5.5)
IgG + IgM + IgA, n (%)	3 (4.1)
IgG + C3, n (%)	12 (16.5)
IgM, n (%)	3 (4.1)
IgM + IgA, n (%)	1 (1.4)
IgM + C3, n (%)	19 (26)
IgA + C3, n (%)	2 (2.7)
Full-house pattern, n (%)	5 (6.8)

DISCUSSION

Over the 14-year period analyzed, 100 patients were diagnosed with MPGN unrelated to lupus at our facility and 92 fulfilled the criteria for analysis. Immunofluorescence assay revealed that the vast majority (79.3%) of the MPGN patients in our sample showed immunoglobulin deposition, whereas 9.7% showed C3 deposition without immunoglobulin and 10.8% showed no deposition of immunoglobulins or complements. Infection, mainly by HCV, was the most prevalent associated disease in all groups while schistosomiasis was the second most prevalent in immunoglobulin positive group.

Surprisingly, in spite of the small sample of C3 positive group over immunoglobulin positive, associated infections on diagnosis of MPGN were proportionally distributed. We can speculate that in those patients infections could have triggered dysregulation of complement cascade that is known as the basis of pathogenesis of C3 glomerulopathy. Otherwise, as expected, autoimmune disease was absent from C3 positive group. There is scarce literature data on analysis of MPGN patients according to the new classification. Woo *et al.*¹³ described complement mediated MPGN in 2 patients (4.3%) and immune-mediated MPGN in 39 patients (95.7%) out of 44 diagnosed with MPGN, not distant from our results that shows a predominance of the group with immune complexes.

Considering MPGN associated to HCV, an Italian paper¹⁴ showed a 20% association while in our sample it was 15%. Cryoglobulinemia was present in 54.5% of our HCV positive patients while in literature there are reports 77.7% of incidence.¹⁵ Cryoglobulinemia

in HCV negative and without any other systemic disease besides MPGN was found in only one patient in our casuistic.

Considering autoimmune disease we found association with MPGN in 8 patients out of 92 evaluated. Seven were in the immunoglobulin positive group and 5 of them showed a lupus-like immunofluorescence pattern (full house) negatively tested for lupus antibodies and without any clinical manifestations of lupus. Zand *et al.*¹⁶ found an association with autoimmune diseases other than lupus in 17 (5.5%) patients out of 308 with MPGN diagnosis, the most common being rheumatoid arthritis and Sjögren's syndrome.

MPGN relates to multiple myeloma, lymphoma, and leukemia besides other paraproteinemias are rare.¹⁷ In our sample, 4 patients had also been diagnosed with leukemia, lymphoma or myeloma: 3 in the immunoglobulin positive group and 1 in the C3 positive group. Larsen *et al.*¹⁸ described MPGN related to dysproteinemia patients with negative monoclonal immunoglobulin deposits that were unmasked only after performing immunofluorescence on formalin-fixed paraffin embedded tissue after protease digestion. Thus, they point to the possibility of misdiagnosis in those cases classifying as MPGN with immunofluorescence without immunoglobulin.

In relation to the clinical and laboratory data there was no difference among the three groups, indicating that only the IF is able to differentiate the groups. The data of optical microscopy between the three groups showed only difference in relation to vascular involvement, where the negative IF group had higher incidence than the other. MPGN with negative IF although not reported in the original classification systems, comprises 10.8% of our patients, and it should be seen as a group in which reparative process of thrombotic microangiopathy (TMA) is involved besides other cause.⁶ However, in our patients we could not see any sign of present TMA although associations with systemic disease (infection, dysproteinemia and autoimmune disease) were present in 60% of them.

The number of patients who had glomerular crescent was similar in all groups, with general impairment less than 10% of the glomeruli. In IF we point out that in patients with HCV IgM predominated. Regarding electron microscopy, that the new classification should be performed in group C3 positive, it was not carried out by own difficulties of our service.

The idiopathic etiology that could be accepted in immunoglobulin positive group corresponded to 49.3% of out casuistic, we do not know if electron microscopy could help to find the etiology in this cases.

Progression to ESRD on follow-up was higher in C3 positive group over immunoglobulin positive or IF negative groups (80%, 28.5% and 44.4%, respectively). Nargund *et al.*¹⁹ characterized 51 subjects with complement dominant MPGN and 20 immunoglobulin dominant MPGN showed ESRD and death in 14 patients (27.4%) complement dominant MPGN and in 6 patients (30%) immunoglobulin dominant MPGN during follow up with median of 2 years. Study comparing DDD and C3 glomerulonephritis ESRD occurred in 47% of the DDD and 23% of C3 glomerulonephritis in median follow-up of 28 months.²⁰

CONCLUSION

Our data correlate with the proposed new classification Sethi and Fervenza⁵ in 83.4% of cases. Only in 11 patients who were diagnosed with infectious disease or autoimmune or gammopathy, they were in no immunoglobulin group. However the primary forms (idiopathic) were present in this study by following the guidelines of the new classification. The only clinical and laboratory differences and histology between groups were the largest vascular involvement in negative IF group and worse renal survival in the C3 group.

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