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Antibodies Against M-Type Phospholipase A2 Receptor (PLA2R) in Patients with Primary Membranous Nephropathy and Lupus Nephritis Class V: A Review

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Abstract

Membranous nephropathy (MN) is a very common disease of male adults with nephrotic syndrome. The disease can be primary, when the cause is not known, or secondary associated with infections, drugs, neoplasias and autoimmune systemic diseases, such as systemic lupus erythematosus (SLE). The primary form accounts for 70–80% of the cases. SLE is a common cause of secondary MN affecting young women. The differential diagnosis from primary and lupus MN by clinical and morphological findings can be difficult. The search for autoantibodies against podocyte antigen M-type phospholipase A2 receptor (PLA2R) has demonstrated high positivity in the serum and renal biopsies in the primary MN and negativity in lupus MN (WHO class V). There is a large literature on the role of anti-PLA2R antibody in the diagnosis and follow-up of patients with membranous nephropathy. The aim of this review is to summarize the literature data on the etiopathogenesis of MN and the value of anti-PLA2R antibody screening for the diagnosis and management of patients.

Keywords: primary membranous nephropathy, lupus membranous nephropathy, podocyte antigen M-type anti-phospholipase A2 receptor, podocyte autoantibodies, differential diagnosis, disease activity

1. Introduction

Membranous nephropathy is a frequent cause of nephrotic syndrome in adults. MN can manifest as an autoimmune primary disease or can be secondary to a wide variety of conditions such as infections, neoplasias, drugs and autoimmune diseases. The differential diagnosis

between primary and secondary forms must be made after an extensive clinical and serological investigation. The clinical course of primary MN is variable, some patients have spontaneous remission and others show progressive course to chronic renal failure. There is no specific marker that identifies which patients will develop chronic renal failure. The treatment can be conservative but sometimes immunosuppressive therapy is required. On the other hand, the secondary forms ameliorate after the associate condition is removed [1].

Recently, a new autoantigen in the podocyte membrane, an M-type phospholipase A2 receptor (PLA2R), was discovered in the serum and in the renal biopsies in 70–80% of primary MN patients. The presence of anti-PLA2R in the glomerular capillary walls by immunohistochemistry favors the diagnosis of primary form of MN and excluded the secondary causes. Anti-PLA2R positive has been very rare in the secondary MN. There are many studies showing anti-PLA2R negative in the serum and biopsies of membranous lupus nephritis. The serum titers of anti-PLA2R are usually elevated in the active phase of primary MN and decline in the remission of disease. In this way, the anti-PLA2R antibody has been used in clinical practice in the differential diagnosis of primary and secondary forms as well as in the monitoring of disease progression [2].

2. The disease

Membranous nephropathy is a glomerular disease characterized by diffuse and uniform thickening of the glomerular capillary walls caused by the deposition of immune complexes, which appears by immunofluorescence as granular deposits of IgG and in the ultrastructure as subepithelial deposits [1] (**Figures 1–3**).

It is one of the main causes of primary glomerulonephritis worldwide [3, 4]. In the São Paulo Registry of Glomerulopathies [5] and, in a retrospective epidemiological study conducted in Brazil with 9617 renal biopsies [6], MN was indicated as the second most prevalent primary glomerular lesion. In our service, the incidence is 33% [7]. It mainly affects male adults, between the fourth and fifth decades [8], and is the main glomerulopathy in the elderly [9].

Figure 1. Diffuse thickening of the glomerular capillary walls (HE-200×).

Figure 2. Diffuse granular deposits of IgG in the glomerular capillary walls (IF-200 $\times$).

Figure 3. Electron-dense epimembranous deposits in the glomerular basement membrane. D = deposit, S = spikes, GBM = glomerular basement membrane, P = podocyte, and E = endothelial cell (EM-21,000 $\times$).

MN presents with high levels of proteinuria of insidious appearance. In 70 to 80% of the cases, there is nephrotic syndrome with hypoalbuminemia, hypercholesterolemia and edema. Microscopic hematuria is common, and the presence of hypertension varies around 50% of cases. Renal function is usually preserved; however, chronic renal failure occurs in 40% of cases within 10 years of evolution. The diagnosis of the disease is made by renal biopsy in the clinical suspicion of proteinuria or nephrotic syndrome [10–14].

MN can evolve over the years in different ways, from spontaneous remission to persistence of the nephrotic syndrome with a slow and progressive course for chronic renal failure.

Spontaneous remission occurs in about 25–30%. The progression to renal insufficiency is around 12–18% of the cases [15]. Due to the high rate of spontaneous remission of the disease and the aggressive specific treatment, it is important to identify prognostic factors that are associated with progression to renal failure. Among the prognostic factors, age over 50 years, male gender, presence of arterial hypertension, proteinuria intensity, elevated serum creatinine, advanced glomerular stage and presence of interstitial fibrosis in renal biopsy are indicators of disease progression [10–12, 15].

3. The primary or idiopathic form and etiopathogenic aspects

The cause of MN is unknown in 80% of the cases being considered primary or idiopathic [16].

Since the mid-1950s, the understanding of the etiopathogenic mechanisms of MN in experimental models has been sought. The first formulated hypothesis was the deposition of circulating immune complexes in the kidney.

Heymann et al. [17] reproduced in the rat a glomerular lesion similar to that of human MN. Heymann's active nephritis was induced by the immunization of rats with rat kidney extracts in Freund's adjuvant. The deposits in the glomerular basement membrane were interpreted as resulting from the passive deposition of circulating immune complexes. Subsequent studies have shown that glomerular deposits in the subepithelial region were composed of antigens normally present on the brush border of the proximal tubules and autoantibodies [18]. And in the Heymann's passive nephritis, the same disease was reproduced in the rat, using the injection of the antiserum obtained by immunizing rabbits with brush border proteins of rat kidney [19]. The hypothesis of circulating immune complexes started to be questioned, and a new hypothesis of local formation of immune deposits by an endogenous antigen localized at subepithelial side of glomerular basement membrane and a circulating autoantibody was formulated (*in situ* immune complexes). Kerjaschki and Farquhar [20] subsequently identified the target autoantigen in the mouse, a protein called megalin, located on the brush border of the proximal tubules and on the cytoplasmic membrane of the podocyte.

In conclusion, the findings of the experimental studies demonstrated that the podocyte contributes to the formation of immunodeposits in MN, which has been considered an autoimmune disease.

Since megalin is not present in human podocytes, the antigen(s) involved in the primary human MN remains unknown.

In 2002, Debiec et al. [21] identified the first autoantigen in the human MN in a case of neonatal nephrotic syndrome. The mother with genetic deficiency of neutral endopeptidase (NEP), a normal protein in the podocytes, was immunized by the fetus with normal expression of NEP. The anti-NEP antibodies synthesized by the mother were transferred, via the placenta to the fetus, with formation of *in situ* immunocomplexes in the kidney. This was a rare familial case of human neonatal primary MN by an autoantigen present in the podocyte. However, MN is a very common pathology, and these findings did not explain all cases of the primary form. Subsequently, numerous studies were done in search for other autoantigens responsible for primary

Figure 4. Immunofluorescence staining of PLA2R in glomerular deposits (IF-400 $\times$).

MN. Beck et al. Salant is the responsible for this Research Group kidney from deceased donors, not used in transplantation, to extract glomerular proteins that were used in western blot reaction with circulating antibodies from MN patients. A 185-kD protein was detected in 70% of patients with primary MN, whereas sera from patients with secondary MN or other glomerular diseases did not react with this protein. The protein was identified by spectrometry as a transmembrane type M receptor of secretory phospholipase A2 (sPLA2R). The PLA2R superfamily is a heterogeneous group of proteins and enzymes that is present in normal podocytes and includes the secretory (sPLA2R), cytoplasmic (cPLA2R), and lysosomal (IPLA2R) forms. They are ubiquitous in nature as an intra- and extracellular form, hydrolyze several phospholipids and act in various biological activities [22, 23]. In the biopsies from patients with idiopathic MN, the receptor is located next to IgG4, a place consistent with the localization of the immunocomplexes of idiopathic membranous nephropathy [2] (**Figure 4**).

PLA2R is considered the autoantigen responsible for the development of primary MN in 70–80% of cases, but there were still 20–30% left without a specific marker. In 2014, a group of researchers from several countries demonstrated the presence of thrombospondin type 1, with a 7A domain (THSD7A), another antigenic target in patients with NM that respond for about 10% of the primary cases [24]. More recently, the same group induced MN in animal model with autoantibodies against THSD7A eluted from renal biopsy of a patient with recurrent MN in the allograft [25].

There are reports of other podocyte antigens with antigenic and targeting capacity for autoantibody production, but their role is still uncertain and more studies are needed [26].

In conclusion, the findings of NEP, PLA2R, and THSD7A autoantigens in primary MN demonstrated that subepithelial deposits form in situ through the binding of circulating autoantibodies to autoantigens expressed on the surface of podocytes. Heymann's nephritis was the basis for understanding the pathogenesis of primary MN.

However, the stimulus that initiates the autoimmune response to podocyte antigens with disease development is still unknown.

There is a strong association between idiopathic MN and HLA-DQA1, located on chromosome 6p21, and the presence of the allele would facilitate the formation of autoantibodies against PLA2R. In chromosome 2q24, the gene encoding the M-type receptor of phospholipase A2 (PLA2R1) is located [27].

A genetic predisposition can act as a trigger, the dysfunction in the innate immune response functions as the bullet and the antibody formed against PLA2R the target. As this process initiates, the disease follows its course. Recently, a publication by Ponticelli and Glassock [28] has gathered the main information about the pathogenesis of NM: the presence of the HLA-DQA1 allele predisposes to disease and with PLA2R exposure in the podocyte membrane with characteristic conformation favors its recognition as autoantigen and starts the process of autoimmunization. Cells responsible for regulating the innate immune response, such as dendritic cells, contact with the receptor and presents to CD8+ cells of the adaptive immune response. Thus, there is a production of IgG4 or IgG1 that binds to the receptor in podocytes with formation of in situ immunocomplexes. The conformation of the receptor in the cell is essential to make it more or less antigenic and enable for the formation of autoantibodies.

With the in situ deposition of immunocomplexes, there is activation of the complement system, lesion of the filtration barrier and loss of proteins to the urinary space. The binding of IgG4 to PLA2R determines local activation of the complement via mannose, since IgG4 is not able to activate complement by the classical or alternative pathway, triggering C5 cleavage, and formation of C5a and C5b. C5a can be eliminated in the urine while C5b binds to other components until formation of C5b-9. The C5b-9 fraction of the complement (attack complex) activates the inflammatory response through specific extracellular signaling pathways, with generation of reactive oxygen species induced by massive biosynthesis of NADPH oxyreductase, lipid peroxidation, and degradation of the glomerular basement membrane with consequent loss of proteins into the urinary space [29]. There is release of arachidonic acid and eicosanoids with disruption of the actin cytoskeleton of the podocytes and loss of the diaphragm of the filtration barrier, leading to detachment of the podocytes from glomerular basement membrane as well as apoptosis of the podocytes [30]. Persistent proteinuria leads to the intrarenal activation of the renin-angiotensin system with angiotensin II synthesis, which also promotes proinflammatory response, activation of transforming growth factor β (TGF β) and platelet-derived growth factor (PDGF), recruitment of inflammatory cells, and myofibroblastic activation, which promotes interstitial fibrosis with concomitant tubular atrophy and chronic renal failure [31].

Studies have been shown that proteinuria, in addition to being directly related to complement activation, also correlates with the deposits' characteristics, the degree of podocyte lesion and CD8+ cellular response [32].

Regarding the pathogenesis of NM, there are doubts in the pathway that change the conformation of PLA2R making it antigenic, the mechanisms of proteinuria, spontaneous remission and the progression of disease. The understanding of these mechanisms may help to choose the therapeutic options more efficient and different for each phase of the disease.

In conclusion, the pathogenic mechanism leading to the deposition of immunocomplexes in the subepithelial region in idiopathic NM is the formation of immunocomplexes in situ. The expression of phospholipase A2 receptor 1 (PLA2R) on the podocyte membrane is recognized

as an antigenic stimulus, against which an IgG4 or IgG1 is produced, local complement activation, inflammatory and oxidative response, with podocyte disruption and lesion in the filtration barrier with consequent proteinuria.

Ronco and Debiec [33] believe that further studies should be conducted to evaluate whether PLA2R protein in human MN produces podocyte injury similar to the megalin of Heymann's nephritis. The correlation of the anti-PLA2R antibodies with the disease activity and the presence of the PLA2R protein in the immune deposits suggest that they are the cause and not consequence of the podocyte injury. On the other hand, the absence of anti-PLA2R antibodies in other pathologies with proteinuria also shows that these antibodies are not only markers of the disease or of the podocyte lesion [34].

4. The discovery of the PLA2R antigen and the differential diagnosis of the primary and secondary MN

The secondary form of MN is more rare and is related to infections, autoimmune diseases, neoplasias and drugs. In children, hepatitis B is a frequent cause of MN and the treatment of hepatitis with alpha interferon is usually accompanied by remission of proteinuria. Systemic lupus erythematosus (SLE) often courses with glomerulonephritis, and one type of presentation is a membranous form (WHO and ISN/RPS class V). About 10% of MN patients are carriers of neoplasias. The most common sites are gastrointestinal tract, prostate, lung, and breast. The antigen finding in the biopsies of MN patients, such as HBeAg, HBsAg and HBcAg in hepatitis B virus, double helix DNA in SLE and carcinoembryonic antigen (CEA) in gastrointestinal tract neoplasias, suggests a causal relationship between the underlying disease and the manifestation of glomerulonephritis. However, the possibility of association of diseases cannot be ruled out [1].

The investigation of secondary causes with complete clinical examination, serologies and analysis by images is necessary. After excluding secondary forms, the patients with idiopathic MN can receive supportive treatment or an immunosuppressive therapy; in the secondary form, the treatment is directed against the cause of the disease. However, in some patients, MN may appear months or years before the cause is detected. This makes treatment and clinical monitoring difficult.

The discovery of the PLA2R antigen brought a number of benefits for the diagnosis and monitoring of the primary form of the disease. The distinction between the primary and secondary forms was made easier by the detection of the anti-PLA2R autoantibody in kidney biopsy and serum of patients, and extensive procedures for differential diagnosis and unnecessary exposure to immunosuppression may be excluded.

Several studies have been done with the aim of evaluating the sensitivity and specificity of the anti-PLA2R autoantibody in renal biopsy and serum of patients with MN.

In a Chinese study of 60 patients with primary and 46 patients with secondary MN, a specificity of 89% [35] was demonstrated. In the Iranian population, anti-PLA2R was detected in 74% of patients with primary MN and was absent in the secondary form [36].

5. Relationship between anti-PLA2R antibodies and the disease activity

After the discovery of the PLA2R antigen, studies have sought to establish greater relationships between the anti-PLA2R antibody and the disease's immune activity. The association between antibody titer and disease activity is clear [37]. Two techniques for evaluating anti-PLA2R serum antibody are described by immunofluorescence or the ELISA method [38–41]. The immunofluorescence test is more sensitive and semiquantitative, while the ELISA test is faster to do and the values are quantitative, which allows a better evaluation of the evolution of its levels [38].

In a European cohort study, 14 of 18 patients (78%) with primary MN had anti-PLA2R antibodies in serum [37]. Segarra-Medrano et al. [42] found a prevalence of anti-PLA2R of 76.6% in patients with idiopathic MN against 5.8% with secondary MN; the sensitivity of the immunohistochemical reaction in the renal biopsy was 76.6% and the specificity 94.2%. Serum antibody testing showed similar sensitivity and specificity between Elisa and immunofluorescence reactions (sensitivity: 72.3 × 74.4 and specificity: 94.2 × 94.2, respectively). In another study, Segarra-Medrano et al. [43] showed a greater reduction in antibody titers in the patients with remission of disease. In a prospective study, Hoxha et al. [44] showed in 61 of the 88 patients (69%) with MN a marked deposition to PLA2R with subepithelial location. Of the 61 patients, 98.4% had antibodies in the serum. This prospective study shows a close correlation between biopsy and serum positivity; negative reaction in the biopsy is accompanied by the absence of antibodies in the serum. Performing kidney biopsies and serum tests at different times may result in discrepant results. The serum may be negative in the treatment period, and the biopsy may remain positive. The analysis of the biopsy is, therefore, important to confirm the diagnosis of primary MN. Debiec and Ronco [45] also discuss the divergent results between serum and biopsy data; they demonstrated in 42 patients a serum and biopsies sensitivity of 57 and 74%, respectively. Of the 42 patients, 21 presented PLA2R positivity in serum and biopsy; in 3 patients, the study was positive in the serum and negative in the biopsy; in 18 patients, the biopsy was positive and the serum negative. The presence of PLA2R in the serum in the absence of deposition in the kidney suggests non-nephritogenic antibody or difficult access to the antigenic epitopes. The fast clearing of serum antibodies or late search in the course of treatment may explain the positivity in the biopsy with negative serology. Although proteinuria levels are slightly higher in PLA2R-positive patients [44, 46] and decrease during treatment and disease remission, levels of anti-PLA2R antibodies usually decrease months before proteinuria, indicating that protein loss in urine is primarily a result of structural injury of the glomerular basement membrane by inflammation and not only by the deposition of immunocomplexes.

Svobodova et al. [47] advocate the idea that the analysis of biopsies is very important for the diagnosis of primary MN mainly in retrospective studies. When serum is not available or there was clearing of the antibodies in the remission phase of the disease, the biopsy plays a key role in the diagnosis. When serum samples are collected after a long time of biopsy and during disease remission, the serum positivity is 22 vs. 59% in the biopsy.

In conclusion, the close relationship between antibody titers in the serum of patients with idiopathic NM and proteinuria has been recently demonstrated and allows interpreting that the decline of the antibody predicts remission of the disease. In the study, following the

initiation of specific immunosuppressive therapy, there was a progressive reduction in circulating antibody levels in the first 3 months, followed by a slow but progressive reduction of proteinuria levels, which reached their lowest value after about 9 months of onset of follow-up. Thus, it can be stated that the reduction in the antibody precedes in months the reduction of proteinuria, and that it is associated with the time to reach remission [46].

Patients with increasing anti-PLA2R antibody titers are less prone to spontaneous remission, which, together with nephrotic proteinuria, would suggest to use immunosuppression, and patients with progressive reduction of antibody levels, which could be clinically followed, can evolve with spontaneous remission [48]. During the follow-up of the patients, the dosage of the anti-PLA2R antibody brings great contributions. The quantitative and evolutionary evaluation of the antibody can predict spontaneous remission in months, thus avoiding the initiation of specific treatment in patients with greater chances of remission. In cases where there is an increase in anti-PLA2R antibody levels, there is a greater chance of progression, which would suggest the initiation of specific treatment, avoiding waiting and decreasing the chance of disease progression during this period.

The close correlation of the serum levels of the anti-PLA2 R autoantibodies with the immunological activity of the disease allows the monitoring of the treatment and evaluation of the prognosis. Patients who present remission of the disease after treatment show a reduction in antibody titers and proteinuria levels [35, 37, 44, 49] and an increase with relapse [37]. A prospective study shows that the reduction in anti-PLA2R antibody titers is greater in patients' remission of the disease. Monitoring of antibody titers after initiation of treatment is useful in estimating the time to remission of the disease [43]. Beck et al. [49] evaluated the relationship between levels of the anti-PLA2R antibody and response to Rituximab treatment. Titers decreased in most patients and anticipated a decrease in proteinuria.

6. Antibodies to M-type phospholipase A2 receptor (PLA2R) and membranous lupus nephritis

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease affecting multiple organ systems. The lupus nephritis has many forms of clinical manifestations and causes the greatest risks of morbidity and mortality. The renal biopsy plays an important role in the management of patients with SLE. The lupus nephritis classifications, based on renal pathologic findings, show a wide variety of morphologic expressions, and several classifications of lupus nephritis have been proposed. A pure membranous form or class V for lupus nephritis by OMS and ISN/RPS classifications shows similar morphologic findings from idiopathic MN and accounts for 8–29% of biopsy series. The presence of C1q by immunofluorescence, some degree of mesangial hypercellularity, and small focal subendothelial deposits are helpful to differentiate from idiopathic MN [50]. Differently from proliferative forms of lupus nephritis, the patients with a membranous lupus nephritis may present with a normocomplementemic kidney limited disease. The lupus membranous nephritis may precede by years a clinical diagnosis of SLE and can initially be diagnosed as idiopathic MN [51, 52]. Specific

Authors (y)	MN-PLA2R (+)			Lupus MN-PLA2R (+)		
	n	Biopsy	Serum	n	Biopsy	Serum
Beck et al. [2]	37	26 (70%)	26 (70%)	6	0	0
Qin et al. [35]	60	ND	49 (82%)	20	ND	1 (5%)
Hoxha et al. [44]	88	61 (69%)	60 (68%)	5	0	0
Gunnarsson et al. [54]	3	ND	3 (100%)	25	ND	0
Ardalan et al. [36]	23	ND	17 (74%)	1	ND	0
Oh et al. [55]	100	ND	69 (69%)	1	ND	0
Svobodova et al. [47]	65	45 (69%)	26 (40%)	16	0	ND
Segarra-Medrano et al. [42, 43]	47	37 (76%)	45 (97%)	8	0	0
Xie et al. [56]	—	86/102 (84%)	24/41 (58%)	—	1/38(2.6%)	0/13
Dong et al. [57]	179	165 (92%)	ND	40	0	ND
Kimura et al. [58]	25	10/19 (52%)	12/25(48%)	13	0	0

ND: not done.

Table 1. Comparisons between PLA2R (+) in primary membranous nephropathy (MN) and lupus membranous nephropathy (lupus MN).

serologic markers for membranous lupus nephritis are limited, and a biopsy is required to discriminate between different forms of lupus nephritis as well as other types of kidney disorders. Only antibodies to ribosomal P proteins, in the absence of anti-double-stranded DNA antibodies, have been found to associate with pure membranous lupus nephritis [53]. Although idiopathic membranous nephritis and membranous lupus nephritis have clinical and histopathologic similarities, the different autoantibody profiles suggest different pathogenic mechanisms. Many studies confirm the absence of PLA2R antibodies in membranous lupus nephritis, and its determination is a noninvasive tool to discriminate from idiopathic MN (Table 1).

7. Conclusions

Membranous nephropathy is one of the main causes of primary glomerulonephritis worldwide. It mostly affects male adults with nephrotic syndrome. The binding of circulating autoantibodies to autoantigens expressed on the surface of podocytes forms immunocomplexes in situ and subepithelial deposits in the glomerular basement membrane. M-type phospholipase A2 receptor on the podocyte membrane is an antigenic stimulus in 70–80% of primary MN and absent in most of the secondary forms of membranous nephropathy. Studies have shown that PLA2R antibodies are negative in membranous lupus nephritis, and its determination is a noninvasive tool to discriminate from idiopathic MN. The discovery of the PLA2 R antigen brought a number of benefits for the diagnosis and monitoring of the primary form of the disease. The distinction between the primary and secondary forms was made easier by the detection of the anti-PLA2R

autoantibody in kidney biopsy and serum of patients, and extensive procedures for differential diagnosis and unnecessary exposure to immunosuppression may be excluded. And the serum titers of anti-PLA2R antibodies are useful to determinate the activity of the disease. In NM, a set of biomarkers with potential in establishing diagnosis, prognosis and therapeutic guide has already been identified. The evolution of proteinuria and serum creatinine, coupled with the evolutionary pattern of the anti-PLA2R antibody, is the best guide for the specific therapeutic decision in NM.

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Conflict of interest

No conflict of interest.

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References

- [1] Silva VS, Hagemann R, Viero RM. Nefropatia membranosa. In: Barros RT, Ribeiro Alves MAVF, Dantas M, Kirsztajn GM, dos Santos Sens YA, editors. *Glomerulopatias-Patogenia*. 3rd ed. São Paulo: Clínica e Tratamento, Sarvier; 2012; pp. 233-276
- [2] Beck LH, Bonegio RGB, Lambeau G, Beck DM, Powel DW, Cummins TD, Klein JB, Salant DJ. M-type phospholipase A₂ receptor as target antigen in idiopathic membranous nephropathy. *The New England Journal of Medicine*. 2009;**361**(1):11-21

- [3] Schena FP. Survey of the Italian Registry of renal biopsies. Frequency of renal diseases for 7 consecutive years. *Nephrology, Dialysis, Transplantation*. 1997;**12**:418-426
- [4] McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: A systematic review of the literature. *Nephrology, Dialysis, Transplantation*. 2011;**26**:414-430
- [5] Malafronte P, Mastroiani-Kirsztajn G, Betônico GN. Paulista registry of glomerulonephritis: 5-year data report. *Nephrology, Dialysis, Transplantation*. 2006;**21**:3098-3105
- [6] Polito MG, de Moura LA, Kirsztajn GM. An overview on frequency of renal biopsy diagnosis in Brazil: Clinical and pathological patterns based on 9617 native kidney biopsies. *Nephrology, Dialysis, Transplantation*. 2010;**25**:490-496
- [7] Soares VA, Franco RJS, Monteiro-Filho RC, Viero RM, Almeida DB. Estudo do quadro clínico de 121 pacientes portadores de glomerulopatias-síndrome nefrótica. *Jornal Brasileiro de Nefrologia*. 1983;**5**:118-112
- [8] Gartner HV, Watanabe T, Ott V, Adam A, Bohle A, Edel HH, Kluthe R, Renner E, Scheler F, Schmulling RM, Sieberth HG. Correlations between morphological and clinical feature in idiopathic epimembranous glomerulonephritis. A study of 403 biopsies of 367 patients. *Current Topics in Pathology*. 1977;**65**:1-29
- [9] Davison AM, Johnston PA. Glomerulonephritis in the elderly. *Nephrology, Dialysis, Transplantation*. 1996;**11**(9):34-37
- [10] Ramzy MH, Cameron JS, Turner DR, Neild GH, Ogg CS, Hicks J. The long-term outcome of idiopathic membranous nephropathy. *Clinical Nephrology*. 1981;**16**:13-19
- [11] Murphy BF, Fairley KF, OS K-S. Idiopathic membranous glomerulonephritis: Long-term follow-up in 139 cases. *Clinical Nephrology*. 1988;**30**:175-181
- [12] Sampaio M, Balbi AL, Martin LC, Chio CS, Cheide L, Pereira ACC, Bignardi JH, Viero RM, Soares VA. Glomerulonefrite membranosa idiopática: história natural e fatores prognósticos. *Nefrologia Latinoamericana*. 1995;**2**:175-183
- [13] Wasserstein AG. Membranous glomerulonephritis. *Journal of the American Society of Nephrology*. 1997;**8**:664-674
- [14] Glasscock RJ. Diagnosis and natural course of membranous nephropathy. *Seminars in Nephrology*. 2003;**23**:324-332
- [15] Donadio Jr JV, Torres VE, Velosa JA, Wagoner RD, Holley KE, Okamura M, Ilstrup DM, Chu CP. Idiopathic membranous nephropathy: The natural history of untreated patients. *Kidney Int*. 1988;**33**:708-715
- [16] Noël LM, Zanetti M, Droz M, Barbanel C. Long-term prognosis of idiopathic membranous glomerulonephritis: Study of 116 untreated patients. *The American Journal of Medicine*. 1979;**66**:82-90
- [17] Heymann W, Hackel DB, Hawood S, Wilson SG, Hunter JL. Production of nephritic syndrome in rats by Freund's adjuvant and rat kidney suspensions. *Proceedings of the Society for Experimental Biology and Medicine*. 1959;**100**:660-664

- [18] Cybulsky AV, Quigg RJ, Badalamenti J, Salant DJ. Anti-Fx1A induces association of Heymann nephritis antigens with microfilaments of cultured glomerular visceral epithelial cells. *The American Journal of Pathology*. 1987;**129**:373-384
- [19] Feenstra K, Van Den Lee R, Greben HA, Arends A, Hoedemaker PJ. Experimental glomerulonephritis in the rat induced by antibodies directed against tubular antigens. I. The natural history: A histologic and immunohistologic study at the light microscopic and the ultrastructural level. *Laboratory Investigation*. 1975;**32**(2):235-242
- [20] Kerjaschki D, Farquhar MG. Immunocytochemical localization of the Heymann nephritis antigen (gp330) in glomerular epithelial cells of normal Lewis rats. *The Journal of Experimental Medicine*. 1983;**157**:667-686
- [21] Debiec H, Guigonis V, Mougnot B, Decobert F, Haymann JP, Bensman A, Deschenes G, Ronco P. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. *The New England Journal of Medicine*. 2002;**346**:2053-2060
- [22] East L, Isacke CM. The mannose receptor family. *Biochimica et Biophysica Acta*. 2002;**1572**:364-386
- [23] Schaloske RH, Dennis EA. The phospholipase A2 superfamily and its group numbering system. *Biochimica et Biophysica Acta*. 2006;**1761**:1246-1259
- [24] Tomas NM, Beck LH Jr, Mayer-Schwesinger C, Seitz-Polski B, Ma H, Zahner G, Dolla G, Hoxha E, Helmchen U, Dabert-Gay AS, Debayle D, Merchant M, Klein J, Salant DJ, Stahl RAK, Lambeau G. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. *The New England Journal of Medicine*. 2014;**371**(24):2277-2287
- [25] Tomas NM, Hoxha E, Reinicke AT, Fester L, Helmchen U, Gerth J, Bachmann F, Budde K, Koch-Nolte F, Zahner G, Rune G, Lambeau G, Meyer-Schwesinger C, Stahl RAK. Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy. *The Journal of Clinical Investigation*. 2016;**126**(7):2519-2532
- [26] Murtas C, Bruschi M, Candiano G, Moroni G, Magistrini R, Magnano A, Bruno F, Radice A, Furci L, Argentiero L, Carnevali ML, Messa P, Scolari F, Sinico RA, Gesualdo L, Fervenza FC, Allegri L, Ravani P, Ghiggeri GM. Coexistence of different circulating anti-podocyte antibodies in membranous nephropathy. *Clinical Journal of the American Society of Nephrology*. 2012;**7**:1394-1400
- [27] Stanescu HC, Arcos-Burgos M, Medlar A, Bockenhauer D, Kottgen A, Dragomirescu L, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. *The New England Journal of Medicine*. 2011;**364**:616-626
- [28] Ponticelli C, Glassock RJ. Glomerular diseases: Membranous nephropathy—A modern view. *Clinical Journal of the American Society of Nephrology*. 2014;**9**(3):609-616
- [29] Nangaku M, Shankland SJ, Couser WG. Cellular response to injury in membranous nephropathy. *Journal of the American Society of Nephrology*. 2005;**16**:1195-1204
- [30] Kerjaschki D. Pathomechanisms and molecular basis of membranous glomerulopathy. *Lancet*. 2004;**364**:1194-1196

- [31] Mezzano SA, Aros CA, Droguett A, Burgos ME, Ardiles LG, Flore CA, Carpio D, Vio CP, Ruiz-Ortega M, Egido J. Renal angiotensin II up-regulation and myofibroblast activation in human membranous nephropathy. *Kidney International*. 2003;**64**:39-45
- [32] Glassock RJ. The pathogenesis of idiopathic membranous nephropathy: A 50-year odyssey. *American Journal of Kidney Diseases*. 2010;**56**:157-167
- [33] Ronco P, Debiec H. Antigen identification in membranous nephropathy moves toward targeted monitoring and new therapy. *Journal of the American Society of Nephrology*. 2010;**21**(4):564-569
- [34] Beck LH. Monoclonal anti-PLA₂R and recurrent membranous nephropathy: Another piece of the puzzle. *Journal of the American Society of Nephrology*. 2012;**23**:1909-1916
- [35] Qin W, Beck LH, Zeng C, Chen Z, Li S, Zuo K, Salant DJ, Liu Z. Anti-phospholipase A2 receptor antibody in membranous nephropathy. *Journal of the American Society of Nephrology*. 2011;**22**(6):1137-1143
- [36] Ardalan M, Ghafari A, Hamzavi F, Nasri H, Baradaran B, Majidi J, Nikbin B. Anti-phospholipase A2 receptor antibody in idiopathic membranous nephropathy: A report from Iranian population. *Journal of Nephropathology*. 2013;**2**(4):241-248
- [37] Hofstra JM, Beck LH, Beck DM, Wetzels JF, Salant DJ. Anti-phospholipase A receptor antibodies correlate with clinical status in idiopathic membranous nephropathy. *Clinical Journal of the American Society of Nephrology*. 2011;**6**:1286-1291
- [38] Ronco P, Debiec H. Pathophysiological advances in membranous nephropathy: Time for a shift in patient's care. *Lancet*. 2015;**385**:1983-1992
- [39] Hoxha E, Harendza S, Zahner G, Panzer U, Steinmetz O, Fechner K, Helmchen U, Stahl RA. An immunofluorescence test for phospholipase-A2-receptor antibodies and its clinical usefulness in patients with membranous glomerulonephritis. *Nephrology, Dialysis, Transplantation*. 2011;**26**:2526-2532
- [40] Dahnrich C, Komorowski L, Probst C, Seitz-Polski B, Esnault V, Wetzels JF, Hofstra JM, Hoxha E, Stahl RA, Lambeau G, Stocker W, Schlumberger W. Development of a standardized ELISA for the determination of autoantibodies against human M-type phospholipase A2 receptor in primary membranous nephropathy. *Clinica Chimica Acta*. 2013;**421**:213-218
- [41] VanBeek C, Haas M. Anti-PLA₂R-associated membranous nephropathy: A review with emphasis on diagnostic testing methods. *Clinical Nephrology*. 2015;**84**(1):1-9
- [42] Segarra-Medrano A, Jatem-Escalante E, Quiles-Pérez MT, Salcedo MT, Arbós-Via MA, Ostos H, Valtierra N, Carnicer-Cáceres C, Agraz-Pamplona I. Prevalencia, valor diagnóstico y características clínicas asociadas a la presencia de niveles circulantes y depósitos renales de anticuerpos contra El receptor tipo M de La fosfolipasa A2 em nefropatia membranosa idiopática. *Nefrología*. 2014;**34**(3):353-359
- [43] Segarra-Medrano A, Jatem-Escalante E, Carnicer-Cáceres C, Agraz-Pamplona I, Salcedo MT, Valtierra N, Ostos-Roldán E, Arredondo KV, Jaramillo J. Evolution of antibody titre

- against the M-type phospholipase A2 receptor and clinical response in idiopathic membranous nephropathy patients treated with tacrolimus. *Nefrología*. 2014;**34**(4):491-497
- [44] Hoxha E, Kneibler U, Stege G, Zahner G, Thiele I, Panzer U, Harendza S, Helmchen UM, Stahl RAK. Enhanced expression of the M-type phospholipase A2 receptor in glomeruli correlates with serum receptor antibodies in primary membranous nephropathy. *Kidney International*. 2012;**82**:797-804
- [45] Debiec H, Ronco P. PLA₂R autoantibodies and PLA₂R glomerular deposits in membranous nephropathy. *The New England Journal of Medicine*. 2011;**364**:689-690
- [46] Hoxha E, Thiele I, Zahner G, Panzer U, Harendza S, Stahl RAK. Phospholipase A2 receptor autoantibodies and clinical outcome in patient with membranous nephropathy. *Journal of the American Society of Nephrology*. 2014;**25**(6):1357-1366
- [47] Svobodova B, Honsova E, Ronco P, Tesar V, Debiec H. Kidney biopsy is a sensitive tool for retrospective diagnosis of PLA₂R-related membranous nephropathy. *Nephrology, Dialysis, Transplantation*. 2013;**28**:1839-1844
- [48] de VAS, Glassock RJ, Nath KA, Sethi S, Fervenza FC. A proposal for a serology-based approach to membranous nephropathy. *Journal of the American Society of Nephrology*. 2017;**28**(2):421-430
- [49] Beck LH, Fervenza FC, Beck DM, Bonegio RGB, Malik FA, Erickson SB, Cosio FG, Cattran DC, Salant DJ. Rituximab-induced depletion of anti-PLA₂R autoantibodies predicts response in membranous nephropathy. *Journal of the American Society of Nephrology*. 2011;**22**:1543-1550
- [50] D'Agati VD, Barry Stokes M. Renal disease in systemic lupus erythematosus, mixed connective tissue disease, Sjogren syndrome, and rheumatoid arthritis. In: Charles Jennette J, Olson JL, Silva FG, D'Agati VD, editors. *Heptinstall's Pathology of Kidney*. 7th ed. USA: Wolters Kluwer; 2015. pp. 559-656
- [51] Donadio JV Jr, Burgess JH, Holley KE. Membranous lupus nephropathy: A clinicopathologic study. *Medicine (Baltimore)*. 1977;**56**(6):527-536
- [52] Shearn MA, Hopper J Jr, Biava CG. Membranous lupus nephropathy initially seen as idiopathic membranous nephropathy. Possible diagnostic value of tubular reticular structures. *Archives of Internal Medicine*. 1980;**140**(11):1521-1523
- [53] do Nascimento AP, Viana V d S, Testagrossa L d A, Leon EP, Borba EF, Barros RT, Bonfá E. Antibodies to ribosomal P proteins: A potential serologic marker for lupus membranous glomerulonephritis. *Arthritis and Rheumatism*. 2006;**54**(5):1568-1572
- [54] Gunnarsson I, Schlumberger W, Ronnelid J. Antibodies to M-type phospholipase A2 receptor (PLA₂R) and membranous lupus nephritis. *American Journal of Kidney Diseases*. 2012;**59**(4):582-589
- [55] Oh YJ, Yang SH, Kim DK, Kang SW, Kim YS. Autoantibodies against phospholipase A2 receptor in Korean patients with membranous nephropathy. *PLoS One*. 2013;**8**(4):1-8

- [56] Xie Q, Li Y, Xue J, Xiong Z, Wang L, Sun Z, Ren Y, Zhu X, Hao CM. Renal phospholipase A 2 receptor in hepatitis B virus-associated membranous nephropathy. *American Journal of Nephrology*. 2015;**41**:345-353
- [57] Dong HR, Wang YY, Cheng XH, Wang GQ, Sun LJ, Cheng H, Chen YP. Retrospective study of phospholipase A2 receptor and IgG subclasses in glomerular deposits in Chinese patients with membranous nephropathy. *PLoS One*. 2016;**11**(5):e0156263. DOI: 10.1371/journal.pone.0156263
- [58] Kimura Y, Miura N, Debiec H, Morita H, Banno S, Ronco P, Imai H. Circulating antibodies to a-enolase and phospholipase A2 receptor and composition of glomerular deposits in Japanese patients with primary or secondary membranous nephropathy. *Clinical and Experimental Nephrology*. 2017;**21**:117-126