



ORIGINAL ARTICLE

Antiphospholipase 2 receptor antibody levels to predict complete spontaneous remission in primary membranous nephropathy

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Abstract

Background: M-type phospholipase A2 receptor (APLA2R) is considered the major antigen involved in the pathogenesis of adult primary membranous nephropathy (MN), which is the leading cause of non-diabetic nephrotic syndrome. Antibodies to this antigen have been proved to be an excellent biomarker of disease activity in primary MN. In fact, preliminary data suggest that the higher the antibody level the more proteinuria, and that a decrease in antibody level precedes the remission of proteinuria, but more solid evidence is needed.

Methods: The present work aims to characterize the predictive value of the level of antibodies against PLA2R as a biomarker of disease course and treatment response in a well-defined cohort of 62 patients from University Hospitals Clinic of Barcelona and Josep Trueta in Girona. The primary outcome was the appearance of a spontaneous complete remission (CR), defined as induction of a CR without the use of immunosuppressive agents.

Results: In common with other reports, this work confirms that spontaneous CR is more frequent in patients with low titre of APLA2R at diagnosis, but strikingly, in this cohort we found that spontaneous CR was achieved in patients with APLA2R levels <40 UI/mL. Furthermore, spontaneous CR were less frequently observed in patients with proteinuria >8 g/day.

Conclusions: In conclusion, these findings point out the important role of APLA2R as a tool to predict the disease course and establish personalized therapeutic options at the moment of diagnosis of primary MN. Specifically, patients with low titre of APLA2R (<40 UI/mL) and proteinuria <4 g/day could obtain benefit of a longer period of follow-up with conservative treatment after diagnosis.

Key words: antibody, biomarkers, membranous nephropathy, phospholipase A2 receptor, spontaneous remission

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Introduction

Membranous nephropathy (MN) remains the leading cause of nephrotic syndrome in non-diabetic adults, accounting for up to one-third of biopsy diagnoses in many regions [1, 2]. It is a major cause of end-stage renal disease (ESRD) in patients with primary glomerulonephritis, and 40% of untreated patients require renal replacement therapy. MN recurs in 30–50% of recipients of renal transplantation, with graft loss occurring in 50% of patients by 10 years [1–3].

The clinical course of this disease is quite variable; approximately one-third of patients have a complete and spontaneous remission of their proteinuria; one-third experience a partial remission (PR) persisting with subnephrotic range proteinuria; and the remaining third stay nephrotic and progress to ESRD even with immunosuppressive agents [1–4].

The pathogenesis of MN involves *in situ* formation of immune deposits on the outer aspect of the glomerular basement membrane (GBM) resulting in complement activation, cell injury and urinary protein loss [4–6]. These immune deposits are formed by circulating Immunoglobulin (IgG) antibodies specific to endogenous antigens expressed on the podocyte foot processes, or with specificity against circulating cationic or low molecular weight antigens coming from the other side of the GBM [1, 5–8].

In terms of aetiology, MN is most often primary (pMN 80%)—formerly named idiopathic MN—but may be secondary to a variety of conditions, including systemic lupus erythematosus, hepatitis B antigenaemia, malignancy and the use of certain drugs or toxins [1, 5]. It was not until 2009, when antibodies against M-type phospholipase A2 receptor (APLA2R) were discovered, that an underlying cause could be identified to explain the pMN in a great proportion of cases [2–4, 6, 9].

APLA2R is a protein expressed in glomerular podocytes that is considered the major antigen involved in the pathogenesis of adult idiopathic MN (~70%) [2, 10–12]. About 30% of patients with MN have no circulating antibodies against PLA2R (APLA2R), and in those with no evidence of aetiology, it is believed that other endogenous glomerular antigens may be involved in the pathogenesis [2, 3, 5, 10–14]. In recent years, another podocyte autoantigen was found to be involved in adult pMN, the thrombospondin type-1 domain-containing 7A (THSD7A), which is considered the minor antigen, accounting for up to 5% of cases of pMN, although a recent report points out that this kind of antibody is more frequent in patients with MN and neoplasia [5, 6].

These major scientific breakthroughs have been rapidly translated to clinical practice, specifically with the design of an enzyme-linked immunosorbent assay (ELISA) to detect and quantify antibodies against PLA2R, in order to have reliable biomarkers to evaluate disease activity and treatment response [7, 12, 15]. Thus, these antibodies have been studied since they were discovered, proving to have high specificity (~100%), sensitivity (~70–80%) and good predictive value [1, 3, 15]. Furthermore, an association between proteinuria and antibody concentration has been established. The higher the antibody level the more proteinuria, and a decrease in antibody level precedes the remission of proteinuria [1–5, 7–9, 15–19]. Moreover, PLA2R detection in immune complexes at renal tissue is useful for the retrospective diagnosis of pMN, in addition to which the titre of pre-transplant APLA2R could help in the prediction of MN recurrence in kidney transplant recipients or in the prediction of the response to immunosuppressive therapy [1–5, 7–12].

The present work aims to characterize the predictive value of APLA2R levels as a biomarker of disease course and treatment response in a well-defined cohort of pMN patients from University Hospitals Clinic of Barcelona and Josep Trueta in Girona, Cataluña, Spain.

Materials and methods

Study design and patient cohort

The initial population of this observational study consisted of 111 adults >18 years old with biopsy-proven PLA2R antibody pMN from a cohort of patients from Hospital Clinic of Barcelona and Hospital Josep Trueta in Girona, Spain, for whom serum samples were available.

The inclusion criteria were pMN diagnosis established by renal biopsy with the presence of a compatible morphologic pattern, PLA2R detection in immune complexes at renal tissue by immunohistochemistry and no evidence of secondary aetiology. Secondary MN cases were excluded after performing a complete physical examination, serologic studies, autoimmunity, viral serology and thoracoabdominal computed tomography scan, which confirmed the absence of anti-nuclear antibodies, hepatitis B or C serologies, or neoplasia.

Baseline characteristics that were obtained from all patients included APLA2R status, proteinuria, serum creatinine and estimated glomerular filtration rate (GFR) at the time of renal biopsy. Medical records were retrospectively reviewed for outcome.

The study was approved, according to the guidelines of the Helsinki Declaration, by the local ethics committee of the Clinic Hospital in Barcelona. All patients gave written informed consent for their participation.

Renal outcomes

The primary outcome was the appearance of a spontaneous complete remission (CR), defined as induction of a CR without the use of immunosuppressive agents. Secondary outcomes were (i) induced remission, defined as induction of a CR with the use of immunosuppressive agents; (ii) relapse of proteinuria, defined as recurrent proteinuria within the nephrotic range; and (iii) ESRD, defined as the need of renal replacement therapy or GFR <15 mL/min. CR was defined by proteinuria of <0.3 g/day. PR was defined by proteinuria of <2.0 g/day but ≥0.3 g/day.

Quantification of circulating APLA2 was tested for anti-PLA2R IgG antibodies with an ELISA test (EUROIMMUN, Lubeck, Germany), and also, with an indirect immunofluorescence test (IFI) in the initial sample. Positivity for the test was considered with absolute values of ≥14 RU/mL (14 to <20 RU/mL = low positive, >20 RU/mL = positive), according to the manufacturer's recommendations.

Evaluation of clinical parameters

At the moment of the sampling for the ELISA, an analytical profile was performed with measurements of serum total cholesterol, albumin levels, renal function features such as creatinine, 24-h proteinuria and GFR estimated by the MDRD-4 formula.

Nephrotic syndrome was considered when the combination of proteinuria >3.5 g/day, hypoalbuminaemia <3.5 g/dL and hyperlipidaemia were confirmed.

Other relevant features, such as hypertension, diabetes, ischaemic cardiopathy or previous diuretic, blood pressure (BP) medications [angiotensin-converting enzyme inhibitor (ACE

inhibitor)/angiotensin receptor blockers (ARBs)] or immunosuppressive treatment were also recorded.

Data were prospectively collected at three intervals and compiled on standardized forms that included baseline assessments of the patient's laboratory parameters.

Histopathology

A minimum of 10 glomeruli was considered adequate for a biopsy to be included. Standard processing of renal biopsies included light microscopy and IFI. All specimens were stained with haematoxylin and eosin, periodic acid–Schiff, Masson's trichrome and Jones methenamine silver. For IFI, 3µm cryostat sections were stained with polyclonal fluorescein isothiocyanate-conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, lambda, fibrinogen, albumin and C4d, as per routine clinical testing. Paraffin-embedded kidney biopsies were analysed by immunohistochemistry using rabbit affinity-purified specific polyclonal anti-PLA2R antibodies (Atlas Antibodies, Cambridge, UK).

Statistics

Descriptive data are presented as the median or mean [standard deviation (SD)] for continuous variables and as frequency (%) for categorical data. The Mann–Whitney, Kruskal–Wallis and t-test were used for comparisons between groups. Correlation was assessed with Spearman coefficient and outcome data, including the associated risk of recurrence of APLA2R titres, were analysed with Cox regression analysis. Coefficients are expressed as hazard ratios (HRs) with 95% confidence interval (CI). All P-values were two-tailed and were considered significant at <0.05. The software used for the statistical analyses was SPSS 22 version for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics and treatment

Sixty-two patients with pMN with an average of 99 months of follow-up met the inclusion criteria including the PLA2R detection in immune complexes at renal tissue by immunohistochemistry, and had serum samples collected in the three intervals, so they were included in the analysis. The majority of the cohort was male (66.1%) and the average age of onset for the entire cohort was 55 ± 15 years; 30 out of the 62 patients (48%) had complete nephrotic syndrome and 33% patients presented with nephrotic-range proteinuria and preserved kidney function. The mean proteinuria and GFR were 5.96 g/24 h and 87.5 mL/min, respectively. At time of diagnosis, mean serum creatinine was 1.19 mg/dL, mean serum albumin was 3.307 g/L and mean cholesterol was 274.25 mg/dL (Table 1).

Regarding other clinical features, 24.2% suffered from high BP, 4.8% were diabetic and 4.8% had been diagnosed with ischaemic cardiomyopathy.

Anti-PLA2R antibodies in serum were considered positive in 24 of the 62 patients (39%), with a mean value of 108.51 ± 247.23 IU/mL. The test showed a good correlation with the IFI method, which was positive in 24 of 57 patients (42.11%), with a concordance of 100% in the negatives and 91% in the positives. In the renal biopsy, 100% of the patients had positive detection of PLA2R in the immune complexes.

All the patients had clinical follow-up after the diagnosis of at least 6 months, before prescription of immunosuppressive

Table 1. Basal characteristics of the clinical cohort

	n = 62 Mean	σ = SD
Age, years	55	5.12063
Evolution (months) since diagnosis	54.60	2.063
Albumin, g/L	3.307	0.1173
Cholesterol, mg/dL	274.25	14.162
Creatinine, mg/dL	1.1918	0.09693
GFR, mL/min	89.36	5.577
Proteinuria, g/24 h	5.96087	0.685940
APLA2R levels, IU/mL	117.4277	33.96458

treatment following the Toronto score and workflow [7, 8]. Outcome data were available for 56% of patients (n = 62) after a median follow-up of 99 months. During follow-up, four patients (6.45%) did not receive RAS blockage or immunosuppressive drugs, whereas 58 (93%) patients had received BP medication including ACE inhibitors or ARB. Twenty-six out of 58 (44.8%) patients received exclusively conservative therapy, and 55.17% (n = 32) of the patients had received immunosuppressive therapy.

Among this last group of patients who received immunosuppressive therapy 6 patients (19%) received only PDN, 5 patients (16%) received tacrolimus (FK), 2 patients (<1%) received mycophenolate mofetil (MMF) and the 19 remaining patients were given a combination of immunosuppressive agents, including cyclophosphamide (CFM)+Prednisone (19%), FK + PDN (10.5%), CFM + FK (<1%) and other combinations such as FK + CFM + rituximab, FK + MMF + PDN or MMF + FK, which account for the remaining 34%. Table 2 provides differential baseline characteristics among patients treated with conservative therapy versus immunosuppressive therapy.

Remission of proteinuria

Thirty-three (53%) out of 62 patients showed a remission of proteinuria during follow-up; 20 of these had a PR and 13 a CR. Cumulative remission rates were 5, 40 and 55% at 1, 3 and 5 years of follow-up, respectively. Six (18%) remitting patients achieved a CR during conservative therapy only, whereas seven patients (21%) were treated with immunosuppression and achieved a CR after this treatment.

Proteinuria was lower in patients with negative APLA2R ELISA (5.08 ± 0.85) than in those with ELISA positive (8.37 ± 1.4) during the follow-up (P < 0.05) (Figure 1). However, it is worth highlighting that CR was more related to basal APLA2R level than with just the presence of a positive ELISA test. In fact, the appearance of CR during the follow-up was more frequent in patients with APLA2R titre <40 IU/mL (log rank 5.64, P = 0.018) (Figure 2), during the first 5 years. Spontaneous CRs were more frequent in patients with APLA2R levels >40 IU/mL (P < 0.001) and occurred after a median follow-up of 3.1 (95% CI 0.8–5.0) years. Moreover, spontaneous CR rates were higher among both patients with mild and moderate proteinuria as compared with patients with proteinuria >8 g/day.

The basal proteinuria and APLA2R levels were lower in patients that afterwards developed a spontaneous CR during the follow-up, comparing with patients that achieved induced CR (P = 0.00 and P = 0.03, respectively) (Table 3).

Ten out 32 patients who received IS therapy developed PR. Mean age, albumin, clearance, proteinuria and APLA2R levels (baseline) were 45.3 years, 3.1 g/L, 89 mL/min, 6.1 g/day and

Table 2. Differential baseline characteristics among patients treated with conservative therapy versus immunosuppressive therapy

	Conservative therapy (n = 26, M 15, W 11)		Immunosuppressive therapy (n = 32, M 24, W 8)		P-value
	Mean	$\sigma =$ SD	Mean	$\sigma =$ SD	
Albumin, g/L	3.661	0.1476	2.954	0.158	0.02
Cholesterol, mg/dL	252.61	15.923	295.14	22.82	0.13
Creatinine, mg/dL	1.08	0.0978	1.2997	0.165	0.26
Clearance, mL/min	93.21	8.182	85.04	7.551	0.4
Proteinuria, g/24 h	4.85125	0.835	7.25542	1.082	0.08
Ab levels, UI/mL	73.8643	33.068	159.489	58.21	0.2

M, men; W, women; Ab, antibody.

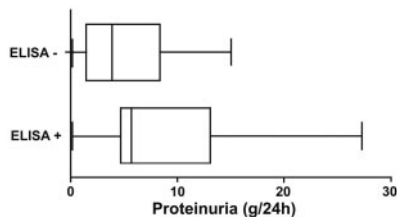


FIGURE 1: Basal proteinuria and APLA2R. Proteinuria was lower in patients with negative APLA2R ELISA (5.08 ± 0.85) than in those with ELISA positive (8.37 ± 1.4) during the follow-up ($P < 0.05$).

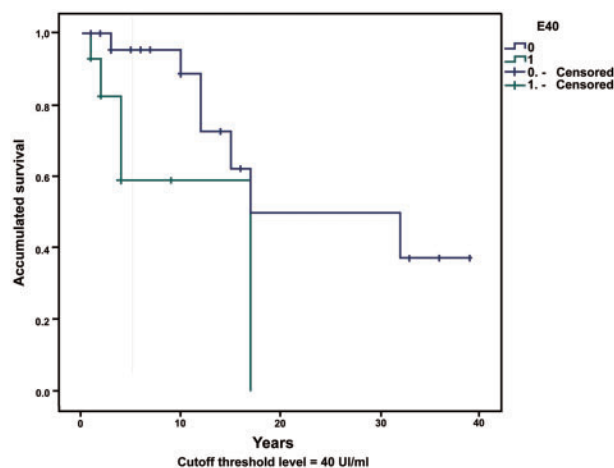


FIGURE 2: Renal survival. CR was related to the antibody level. Cutoff threshold level = 40 UI/mL.

87 IU/mL, respectively, in this group of patients. There were no significant baseline differences between patients with induced complete or partial remission, but there were significant differences in baseline proteinuria and APLA2R levels among patients with spontaneous CR and patients with induced PR (Table 3).

The clinical significance of both APLA2R status and rate of proteinuria was analysed by a multivariate Cox regression. Interestingly, an antibody level <40 IU/mL at baseline was the most pronounced independent predictor of a spontaneous CR: HR was 2.7 (95% CI 1.2–6.0, $P = 0.01$).

ESRD

During follow-up, five patients required renal replacement therapy after a mean follow-up period of 8.3 ± 1.7 (95% CI 3.9–38.6) years. Renal survival was 98.95% after 1.5 years. Of note, renal

survival was statistically significantly better in patients with negative APLA2R during the follow-up (Breslow 5.29, $P = 0.02$) (Figure 3).

Discussion

APLA2R is considered the major antigen involved in the pathogenesis of adult idiopathic MN. This major advance in molecular medicine not only contributes to understanding the pathophysiological basis of MN, but also allows the use of precision medicine for the diagnosis and monitoring of patients with pMN.

In the present study, we found that spontaneous CR rates were higher in patients with PLA2R-related MN with APLA2R levels <40 UI/mL as compared with those patients with higher antibody levels.

Worthy of attention is the fact that spontaneous CR were not present in patients with APLA2R >40 IU/mL and was less frequently observed in patients with proteinuria >8 g/day. Furthermore, patients with high antibody levels had higher risk of developing ESRD, and the necessity of renal replacement therapy was lower in patients with negative APLA2R during the follow-up. Therefore, these findings point out the important role of APLA2R in the clinical prediction of disease course at the moment of diagnosis and suggest that patients with low titre of APLA2R (<40 UI/mL) and proteinuria <4 g/day could benefit from a longer period of follow-up with conservative treatment, and conversely, immunosuppressive treatment has no role in this clinical setting.

Previously, several observational studies related APLA2R levels to the amount of proteinuria and clinical activity [3, 10, 11, 14, 15]. In common with these reports, this work confirms that spontaneous remission is more frequent in patients with low titre of APLA2R, as was reported by other authors [3, 15], but strikingly in this cohort, spontaneous CR almost always was achieved with levels of APLA2R <40 IU/mL. Another relevant finding of this study is the confirmation of prior reports [13, 15, 17] that evaluated the disease course in patients with PLA2R-related MN who were treated with immunosuppression and observed that the decrease of APLA2R preceded the decrease in the amount of proteinuria, suggesting that APLA2R is a good marker of disease activity [18].

In this study, 100% of the patients had positive detection of PLA2R in the immune complexes at renal tissue but only 40% had APLA2R positive in serum, and there were no patients on immunosuppressive therapy at the time of entry on the study. It should be highlighted that cases with negative serum APLA2R but positive PLA2R staining on renal biopsy could be related to an important proportion of patients with early stage of disease or to an immunologically inactive disease, but these hypotheses have to be tested in future prospective studies.

Table 3. Differences in basal proteinuria and APLA2R levels among patients who developed a CR: spontaneous versus induced

	Spontaneous remission		P-value	Induced remission	
	PSR (n = 10, M 6, W 4) Mean (SD)	CSR (n = 6, M 3, W 3)		CIR (n = 7, M 4, W 3) Mean (SD)	PIR (n = 10, M 7, W 3)
Age, years	46 (4.4)	53 (7)	0.692	56 (2.5)	4.3 (5)
Albumin, g/L	3.2 (0.3)	3.3 (0.38)	0.671	3.4 (0.12)	3.1 (0.4)
Ab levels, UI/mL	72 (14)	29 (0.49)	0.003	143 (44)	87 (24)
Proteinuria, g/24h	3 (0.8)	1.4 (0.12)	0.001	4.3 (0.6)	6.1 (0.7)
GFR, mL/min	87 (7)	98 (16)	0.49	84 (7)	89 (6)

Patients with partial induced and spontaneous remission are included as a reference.

PSR, partial spontaneous remission; CSR, complete spontaneous remission; CIR, complete induced remission; PIR, partial induced remission; Ab, antibody; M, men; W, women.

*P-value expresses differences among patients with CR (induced versus spontaneous).

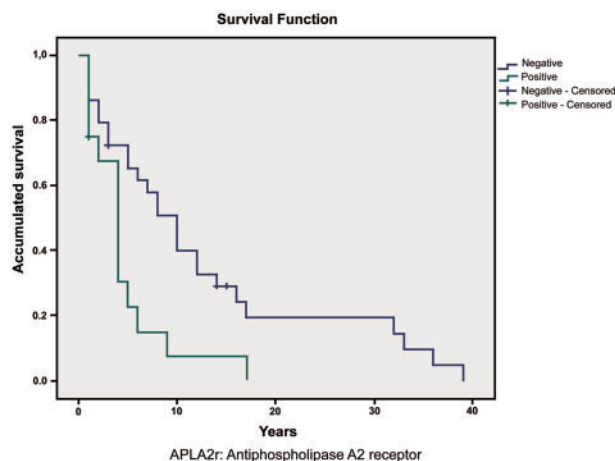


FIGURE 3: Renal survival among different APLA2R statuses.

Because more than half of the patients of this cohort were treated with immunosuppressive agents without taking into account the APLA2R level (samples were collected prospectively but analysed retrospectively), these data do not allow concluding that antibody levels can help to identify patients who will develop spontaneous remission in this specific group of patients.

Since the clinical course of pMN is very variable and many patients with mild disease undergo spontaneous remission and immunosuppressive drugs have important toxicity, currently the decision to treat is based upon the probability that the patient will have progressive disease, defined in the Toronto Glomerulonephritis Registry study as persistent severe proteinuria for at least 3 months, a reduced creatinine clearance at presentation and a decline in creatinine clearance over the assessed proteinuria period [7, 8].

The present work supports the utility of APLA2R as an important tool that optimizes the prediction power of the Toronto algorithm at the moment of diagnosis, decreasing the uncertainty about the clinical course. This is due to the fact that patients with proteinuria <4g/day and APLA2R level <40IU/mL are more prone to develop a spontaneous CR and should benefit from nephroprotection, and be periodically monitored every 6 months to assess for disease progression.

In accordance with the findings of this study, Jullien et al. recently confirmed in a retrospective French cohort, the role of APLA2R titres as a promising tool for the early identification of patients likely to achieve spontaneous remission, with a chance

of remission three times higher in patients from the lowest titre of antibody [20].

Conversely, patients with nephrotic-range proteinuria and high levels of APLA2R (not estimated by this observational study) at the moment of diagnosis should benefit from early treatment in the next 3 months, in order to decrease the antibody titre as soon as possible and then induce remission of proteinuria.

This study is limited by its retrospective design, despite prospective serum collection from two centres. The findings described in the present work need to be validated in a prospective and variable multi-centric cohort of patients.

Very little is known about the earliest stages of human MN because biopsies are typically taken once the disease is more established. Despite the major and rapid progress made in elucidating the mechanisms of pMN, much work remains to be done before we can set up completely the kinetics of APLA2R during the course of pMN. Many unanswered questions remain, and in the next few years, randomized controlled trials should clarify if serum APLA2R antibody profiles reliably predict response to therapy, specifically if patients with higher antibody levels should be treated earlier and independently of renal function, than those with lower titres. In accordance with the results of this work, De Vriese et al. have proposed recently that low baseline and decreasing anti-PLA2R antibody levels strongly predict spontaneous remission, thus favouring conservative therapy. They also suggested that an individualized serology-based approach could optimize efficacy and safety of treatment, and that levels at completion of therapy may forecast long-term outcome [21]. This novel proposal has been also adopted in more recent review by Couser that strongly recommended an antibody-guided diagnosis and treatment algorithm for pMN [22].

In conclusion, APLA2R levels at the time of diagnosis are of predictive value in patients with PLA2R-related MN. Levels of <40 IU/mL are associated with spontaneous CR in this cohort of patients and represent another step towards a more personalized care in this organ-specific, antibody-mediated, autoimmune glomerular disease.

Conflict of interest statement

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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