Noninvasive Diagnosis of PLA2R-Associated Membranous Nephropathy
A Validation Study

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Abstract

Background and objectives Kidney biopsy is the current gold standard to diagnose membranous nephropathy. Approximately 70%–80% of patients with primary membranous nephropathy have circulating anti-phospholipase A2 receptor antibodies. We previously demonstrated that in proteinuric patients with preserved eGFR and absence of associated conditions (e.g., autoimmunity, malignancy, infection, drugs, and paraproteinemia), a positive anti-phospholipase A2 receptor antibody test by ELISA and immunofluorescence assay confirms the diagnosis of membranous nephropathy noninvasively. These data have not been externally validated.

Design, setting, participants, & measurements The clinical and pathologic characteristics of patients with a positive anti-phospholipase A2 receptor antibody test at the Mayo Clinic, the University Hospital Vall D’Hebron (Barcelona), and the Columbia University Medical Center (New York) were retrospectively reviewed. Biopsy findings and presence or absence of a potential associated condition were assessed.

Results From a total of 276 patients with positive anti-phospholipase A2 receptor serology, previously reported patients (n=33), kidney transplant recipients (n=9), pediatric patients (n=2), and patients without kidney biopsy (n=69) were excluded. Among the 163 remaining patients, associated conditions were identified in 47 patients, and 15 patients had diabetes mellitus. All 101 patients of the final cohort had a primary diagnosis of membranous nephropathy on kidney biopsy. In the 79 patients with eGFR ≥60 ml/min per 1.73 m², none of the biopsy findings altered diagnosis or management. Among the 22 patients with decreased eGFR, additional findings included superimposed acute interstitial nephritis (n=1).

Conclusions In patients with preserved eGFR and absence of associated conditions or diabetes, a positive anti-phospholipase A2 receptor test by either ELISA >20 RU/ml or a positive immunofluorescence assay confirms the diagnosis of membranous nephropathy, precluding the requirement for a kidney biopsy.

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Introduction

Membranous nephropathy is the most common cause of nephrotic syndrome in adults. Primary membranous nephropathy is caused by circulating autoantibodies against the podocyte surface antigen M-type phospholipase A2 receptor (PLA2R) (1) in 70%–80% of cases. Thrombospondin type 1 domain-containing 7A (2), semaphorin 3B, neural EGF-like 1 protein, and protocadherin 7 are more recently described target antigens (3–5). Secondary membranous nephropathy occurs in the context of malignancy, systemic autoimmunity, infection, or medication. Increased podocyte expression of exostosin 1/exostosin 2 and neural cell adhesion molecule 1 has been described in patients with membranous nephropathy, the majority of whom have systemic autoimmunity (6–8). Of these target antigens, the most studied, tested, and understood is PLA2R. PLA2R antibody titers correlate well with disease activity (9) and predict remission, relapse, and response to treatment (10). A formal pathogenic role for PLA2R antibodies was recently suggested by the demonstration that rabbit-derived anti-PLA2R IgG induced proteinuria and primary membranous nephropathy in a transgenic murine model (11,12).

Kidney biopsy is the gold standard for diagnosing membranous nephropathy. However, it is expensive, invasive, time consuming, and it can have severe complications. Major complication rates are reported to range from 0.9% (13) to 4% (14), with higher complication rates in hospitalized patients (15). Patients with membranous nephropathy have a higher risk of thromboembolic events than those with other nephrotic conditions and often require anticoagulation at presentation, providing an additional risk with performing a kidney biopsy. Hence, a reliable noninvasive diagnostic test would be extremely useful (16).
Commercially available tests for PLA2R antibodies include a quantitative ELISA and a semiquantitative immunofluorescence assay. We previously demonstrated that all patients with a positive PLA2R test by both ELISA and immunofluorescence assay had membranous nephropathy on kidney biopsy (17). In the subgroup of patients with preserved kidney function and absence of associated conditions, kidney biopsy did not reveal additional information that could alter the diagnostic workup or therapeutic approach. As a result, the recent Kidney Disease Improving Global Outcomes controversies conference suggests that a biopsy can be avoided in certain low-risk scenarios (18). In this study, we sought to validate our findings further by expanding the cohort from the Mayo Clinic and including patients from the University Hospital Vall D’Hebron (VHM; Barcelona, Spain) and the Columbia University Medical Center (CUMC; New York, NY).

Materials and Methods

Participants
Patients who had a serum PLA2R antibody test at one of the Mayo Clinic’s three sites in Minnesota, Arizona, and Florida from July 2018 to July 2020; at VHM from January 2015 to December 2020; and at CUMC from December 2014 to December 2020 were reviewed. Adult patients with a positive PLA2R test and availability of a native kidney biopsy were selected for further study. The study was approved by appropriately authorized ethics committees at all participating sites.

Demographic characteristics, kidney function, proteinuria, and medication history at presentation were recorded. Kidney function was assessed using serum creatinine and eGFR using the Chronic Kidney Disease Epidemiology Collaboration calculation. Patients were stratified by eGFR ≥60 or <60 ml/min per 1.73 m². Medical records were searched for evidence of conditions typically associated with membranous nephropathy, such as malignancy, autoimmune disease, or infectious disease; for offending drugs, such as nonsteroidal anti-inflammatory drugs; and for the presence of diabetes mellitus. Laboratory data were reviewed for antinuclear antibodies, antituble-stranded DNA antibodies, other autoimmune serology, complement factors, hepatitis serology, and paraproteinemia evaluation.

Serology
Serum PLA2R antibody testing was performed utilizing the commercially available Euroimmun Immunofluorescence Assay and ELISA (Euroimmun US, Inc., Mountain Lakes, NJ). Immunofluorescence assay results were reported as positive, negative, or indeterminate (due to high background); ELISA results were reported in relative units (RU) per milliliter. For the patients from the Mayo Clinic, a positive PLA2R test was defined as both positive immunofluorescence assay and ELISA titer ≥2 RU/ml (17). For patients at VHM, a positive PLA2R test was defined as an ELISA titer ≥20 RU/mL. In the CUMC cohort, PLA2R positivity was defined as either a positive immunofluorescence assay or ELISA titer ≥20 RU/ml, as simultaneous testing was not performed at this institution.

Biopsies
Kidney biopsies were processed according to standard techniques for light microscopy, immunofluorescence, and electron microscopy. Biopsies were reviewed for histologic features, such as mesangial and endocapillary proliferation on light microscopy; full-house staining (IgG, IgA, IgM, κ, λ, C3, and C1q) on immunofluorescence; and tubuloreticular inclusions, subendothelial deposits, or mesangial deposits on electron microscopy. PLA2R staining was performed when possible. The total renal chronicity score (TRCS) was quantified as previously described (19).

Statistical Analyses
Depending on the normality of data distribution, continuous variables are presented as mean and SD or median and interquartile range. For comparisons of categorical variables between groups, the Pearson chi-squared test was used, and the results are reported as count and percentage. The two-way independent t-test or the Mann-Whitney U test was used for continuous variables whenever deemed appropriate. A P value of 0.05 was considered significant. All analyses were performed using SPSS 25 (IBM Corp. Released 2017; IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, NY).

Results
During the study period, a total of 3879 PLA2R antibody tests were ordered in 2313 unique patients, yielding 210 positive results in the combined Mayo Clinic and VHM cohorts. In the CUMC cohort, 190 patients had a native biopsy diagnosis of membranous nephropathy. Of these, 125 had a serologic PLA2R test performed, of which 66 of 125 had a positive PLA2R test by either positive immunofluorescence assay (n=49) or ELISA >20 RU/ml (n=7).

Of the 276 patients who met the criteria for positive PLA2R testing, previously reported patients (n=33), kidney transplant recipients (n=9), pediatric patients (n=2), and patients without available biopsy information (n=69) were excluded (Figure 1 shows the combined cohorts, Supplemental Figures 1–3 show the individual cohorts). In 62 patients, diabetes (n=15) or an associated disease (n=47) was identified, including autoimmunity (n=17), malignancy (n=10), nonsteroidal anti-inflammatory drugs (n=7), hepatitis (n=6), paraproteinemia (n=5), or a combination of paraproteinemia and malignancy (n=1). The final cohort consisted of 101 patients with a positive PLA2R antibody test and absence of associated disease and diabetes (Figure 1). When stratified by eGFR, 79 patients (78%) had preserved kidney function as defined by eGFR ≥60 ml/min per 1.73 m², and 22 patients (22%) had eGFR <60 ml/min per 1.73 m². Patients with impaired GFR were significantly older than patients with normal kidney function (Table 1). At the Mayo Clinic and VHM, most of the patients were White, whereas the CUMC cohort was ethnically more diverse, composed of 33% White, 16% Black, 7% Hispanic, and 9% Asian ethnicities; 35% of the patients had declined or unknown race (Supplemental Table 1).

On kidney biopsy, all 101 patients had a primary diagnosis of membranous nephropathy. Among the 79 with
preserved kidney function, none of the additional findings on biopsy altered management (Table 2). One patient had focal glomerular basement membrane duplication but no systemic evidence of thrombotic microangiopathy, such as thrombocytopenia or hypocomplementemia. This patient received induction with cyclophosphamide and was maintained on cyclosporin. At last follow-up, serum creatinine was 1.2 mg/dl, PLA2R was undetectable, and proteinuria was 1.8 g/24 h. Three patients showed capillary glomerular thrombi, of which one patient had a kidney vein thrombosis and none demonstrated evidence of ongoing thrombotic microangiopathy. Among the 22 patients with eGFR<60 ml/min per 1.73 m², additional findings included FSGS (n=2), acute tubular injury (n=2), and acute interstitial nephritis (n=1) (Table 2).

A higher proportion of patients had mesangial/endocapillary proliferation in the CUMC and VHM cohorts compared with the Mayo Clinic cohort, and the VHM cohort had a higher TRCS compared with the other cohorts (Supplemental Table 2).

Discussion
In this multicenter, observational study, we describe 79 patients with biopsy-confirmed membranous nephropathy, preserved kidney function, absence of associated conditions and diabetes, and positive PLA2R serology by either ELISA or immunofluorescence assay (16), adding to the 60 patients with these characteristics that we described previously (17). In none of these patients, kidney biopsy revealed management-changing information other than the diagnosis of membranous nephropathy. These data lend independent support to our previous findings that kidney biopsy in adults does not add any significant information justifying its indication in this group of patients. There are no corresponding data in children.
Athy and FSGS lesions had no difference in kidney function suppression. Of note, patients with membranous nephropathy that an FSGS lesion in merular diseases. In 2006, Troyanov example, an FSGS lesion/scar can be present in many glo- 

Proponents of mandatory kidney biopsy would argue that biopsy may show additional lesions that may be important to guide treatment or alter prognosis. For example, an FSGS lesion/scar can be present in many glomerular diseases. In 2006, Troyanov et al. (20) demonstrated that an FSGS lesion in "idiopathic membranous nephropathy" at presentation was associated with lower creatinine clearance but did not correlate with proteinuria at presentation. During follow-up, patients with FSGS lesions were more likely to receive angiotensin-converting enzyme inhibitor/angiotensin receptor blocker but similar immuno-suppression. Of note, patients with membranous nephropathy and FSGS lesions had no difference in kidney function decline or response to therapy (20). Taken together, a superimposed FSGS lesion does not alter prognosis or management in membranous nephropathy.

Another motivation to perform a kidney biopsy may be to determine the degree of chronicity. However, Troyanov et al. (20) showed that creatinine clearance at presentation was associated with the degree of chronicity but did not preclude remission of proteinuria among patients who received immuno-suppression. Hence, a proper determination of kidney function with a 24-hour creatinine clearance adding to age and BP could be useful to estimate chronic kidney injury (20).

Further review of the pathology findings shows a higher TRCS in the decreased kidney function group, which is

| Table 1. Characteristics of 101 patients with positive anti-phospholipase A2 receptor antibodies and no evidence of associated disease or diabetes |
|--------------------------------------------------|------------------|------------------|------------------|
| Patient Characteristics | All Patients, n=101 | eGFR≥60 ml/min per 1.73 m², n=79 | eGFR<60 ml/min per 1.73 m², n=22 |
| Age (yr) | 51 (39–64) | 49 (37–60) | 61 (50–70) |
| Sex (men), % (no.) | 58 (59/101) | 62 (49/79) | 45 (10/22) |
| Race (White), % (no.) | 62 (63/101) | 59 (47/79) | 73 (16/22) |
| PLA2R titer, RU/mla | 81 (32–200) | 77 (27–219) | 94 (59–188) |
| PLA2R immunofluorescence assay positive, % (no.)³ | 100 (79/79) | 100 (63/63) | 100 (16/16) |
| Creatinine, mg/dl | 0.9 (0.7–1.2) | 0.9 (0.7–1.0) | 1.4 (1.2–1.8) |
| eGFR, ml/min per 1.73 m² | 86 (63–101) | 90 (78–105) | 48 (37–57) |
| Serum albumin, g/dlb | 2.4 (1.9–3.0) | 2.4 (1.9–2.9) | 2.8 (2.1–3.3) |
| Proteinuria, g/24 h² | 8.2 (4.6–12.0) | 7.6 (4.5–12.0) | 9.0 (5.0–12.4) |
| Membranous nephropathy on biopsy, % (no.)³ | 100 (101/101) | 100 (79/79) | 100 (22/22) |
| Additional characteristics | | | |
| GBM, glomerular basement membrane; ATI, acute tubular injury; AIN, acute interstitial nephritis. |

³ELISA was performed in 68 of 101 patients with eGFR≥60 ml/min per 1.73 m² and 16 of 22 with eGFR<60 ml/min per 1.73 m².

For continuous variables, results are expressed as median (interquartile range); for discontinuous variables, results are expressed as percentage (number). *Data are available for 92 participants; eGFR≥60 ml/min per 1.73 m², 71; eGFR<60 ml/min per 1.73 m², 21. PLA2R, anti-phospholipase A2 receptor; RU, relative units.

²Serum albumin was available in 97 of 101 patients with eGFR≥60 ml/min per 1.73 m² and 22 of 22 with eGFR<60 ml/min per 1.73 m².

²Proteinuria was available in 98 of 101 patients with eGFR≥60 ml/min per 1.73 m² and 21 of 22 with eGFR<60 ml/min per 1.73 m².

Table 2. Biopsy characteristics of 101 patients with positive phospholipase A2 receptor antibodies and no evidence of associated disease or diabetes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Anti-Phospholipase A2 Receptor Positive, n=101</th>
<th>eGFR≥60 ml/min per 1.73 m², n=79</th>
<th>eGFR&lt;60 ml/min per 1.73 m², n=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial/endocapillary proliferation, % (no.)</td>
<td>15 (12/79)</td>
<td>29 (6/21)</td>
<td>5 (1/22)</td>
</tr>
<tr>
<td>Full-house immunofluorescence, % (no.)</td>
<td>1 (1/99)</td>
<td>0 (0/77)</td>
<td>27 (6/22)</td>
</tr>
<tr>
<td>Electron microscopy with secondary features, % (no.)</td>
<td>13 (13/97)</td>
<td>9 (7/76)</td>
<td>25 (5/22)</td>
</tr>
<tr>
<td>Mesangial deposits, % (no.)</td>
<td>11 (11/99)</td>
<td>8 (6/77)</td>
<td>0 (0/22)</td>
</tr>
<tr>
<td>Subendothelial deposits, % (no.)</td>
<td>1 (1/97)</td>
<td>1 (1/75)</td>
<td>0 (0/22)</td>
</tr>
<tr>
<td>Tubuloreticular inclusions, % (no.)</td>
<td>1 (1/97)</td>
<td>1 (1/75)</td>
<td>0 (0/22)</td>
</tr>
<tr>
<td>Total renal chronicity score, mean (SD)b</td>
<td>1.5 (2.0)</td>
<td>1.0 (1.5)</td>
<td>3.4 (2.7)</td>
</tr>
<tr>
<td>Additional findings</td>
<td></td>
<td></td>
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<tr>
<td>FSGS (n=3), focal GBM duplication (n=1), capillary loop fibrin thrombi (n=3), ATI (n=4), AIN (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSGS lesion (n=1), focal GBM duplication (n=1), capillary loop fibrin thrombi (n=3), ATI (n=2), AIN (n=1)</td>
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<td></td>
</tr>
</tbody>
</table>

¹Electron microscopy showing subendothelial, mesangial, and tubular basement membrane electron-dense deposits or the presence of endothelial tubuloreticular inclusions.

²Calculated in 99 of 101 patients with eGFR≥60 ml/min per 1.73 m² and 22 of 22 with eGFR<60 ml/min per 1.73 m².
consistent with prior findings (17), and TRCS has already been shown to correlate with kidney function (19,20). Although one may wonder if increased chronicity may affect response to immunosuppression, prior randomized controlled trials of rituximab in membranous nephropathy did not show any association between the degree of interstitial fibrosis and response to rituximab (20–22). Additional findings on biopsy included 11% of patients with mesangial deposits, which is consistent with prior studies (23), and 18% of patients with either mesangial or endocapillary proliferation and other features, such as subendothelial deposits. Tubuloreticular inclusions were rare, likely because patients with concomitant autoimmune diseases were excluded. Clinicopathologic details of patients with associated causes were recently reported in a cohort of 72 patients with membranous nephropathy associated with autoimmunity, malignancy, drugs, and infections (8).

In one of the 22 patients with decreased kidney function, a superimposed acute interstitial nephritis was diagnosed. The finding of acute interstitial nephritis could warrant additional treatment with steroids or withdrawal of an offending agent and is therefore a clinically relevant, actionable finding.

In our previous work, we found cases of concomitant membranous nephropathy and diabetic kidney disease (17). Furthermore, a study evaluating kidney biopsy findings in 620 patients with diabetes mellitus showed that 37% of patients had diabetic nephropathy alone and that 36% had nondiabetic kidney disease alone, and in 27% of the patients, kidney biopsy showed diabetic nephropathy plus nondiabetic kidney disease (24). As such, we excluded patients with preexisting diabetes given that only a kidney biopsy can provide an accurate diagnosis in a patient with diabetes and proteinuria. A positive PLA2R test, regardless of both immunofluorescence assay and ELISA being positive, should not be considered reliable for a diagnosis of membranous nephropathy in a patient with diabetes and proteinuria; the only way to rule out underlying diabetic kidney disease is by performing a kidney biopsy (17).

Although it is widely accepted that children presenting with nephrotic syndrome likely have minimal change disease and that empirical treatment with corticosteroids without a kidney biopsy is the standard of care, a recent publication from India reported 32 pediatric patients with nephrotic syndrome who received a trial of steroids prior to biopsy and were eventually diagnosed with membranous nephropathy. Four of the 25 patients with primary membranous nephropathy in this cohort had positive PLA2R serology (25), highlighting the usefulness of this biomarker even in the pediatric population.

Our study has several strengths. Although our study population is representative of the demographic most affected by membranous nephropathy, that of men of European descent in their fifth to sixth decade of life, it also included a more diverse patient population from the CUMC cohort, expanding the generalizability of our findings. Although Mayo Clinic utilizes a lower cutoff for the ELISA test than the manufacturer recommends, the combination with the immunofluorescence assay test adds a layer of diagnostic strength. However, because this approach requires the use of both tests simultaneously, we obtained data from VHM and CUMC, which used criteria for serologic testing that are the standard around the world (either positive immunofluorescence assay or ELISA >20 RU/ml). Although this has improved the diversity of our patient cohort, we recognize that data to support its use in patients of African or Asian background are limited. Our study is retrospective in nature and does not have sufficient information to determine outcomes using this strategy.

We provide additional evidence that a positive PLA2R antibody test (either ELISA >20 RU/ml or immunofluorescence assay), in the setting of preserved kidney function and absent potential associated causes and diabetes, renders a kidney biopsy as only serving to confirm the diagnosis of membranous nephropathy. However, if there is decreased eGFR, a potential associated disease, or diabetes, a kidney biopsy is indicated to obtain additional information that could alter further diagnostic workup or management. The cohort utilized in this study, assembled at sites in the United States and Europe, validates—and essentially, replicates—results from our original Mayo Clinic cohort.

Disclosures
S.A. Bobart reports employment with Cleveland Clinic Florida and other interests/relationships as faculty of the GlomCon fellowship. A.S. Bombard reports consultancy agreements with Catalyst, Chemocentryx, Novartis, Otsuka, Silence Therapeutics, and Visterra and receiving honoraria from Alexion, Aurinia, Calliditas, GlaxoSmithKline, Novartis, Principio, Traverne, and UpToDate. A.S. De Vriese reports employment with AZ Sint-Jan; consultancy agreements with Amgen; receiving research funding from Amgen, Kayedence Pharma, and Nattopharma; receiving honoraria from Amgen and Baxter; serving as a scientific advisor or member of Abllynck, Alexion, Amgen, Catenion, and Navigant; and speakers bureau for Amgen and Baxter. F.C. Fervenza reports consultancy agreements with Alexion Pharmaceuticals, Alnylam, ByoCrystal, Takeda, and Novartis; receiving research funding from Chemocentryx, Genentech, Janssen Pharmaceutical, Questcor/Mallinckrodt; and Retrophin; receiving honoraria from UpToDate; and serving as a scientific advisor or member of JASN, Kidney International, Nephrology, Nephrology Dialysis and Transplantation, and UpToDate. S. Sethi reports consultancy agreements with Novartis and receiving honoraria for teaching, grand rounds, lectures, UpToDate, and reviewing slides for a study for Novartis. M.J. Soler reports consultancy agreements with AstraZeneca, Boehringer, Esteve, Jansen, Mundipharma, and Novo Nordisk; receiving research funding from Abbvie and Boehringer; receiving honoraria from AstraZeneca, Boehringer, Esteve, FMC, Jansen, Mundipharma, Novo Nordisk, and Otsuka; patent number U691ES00; serving as a scientific advisor or member of BMC Nephrology, Clinical Kidney Journal, the ERA-EDTA Council (member), and scientific advisory board European Renal Association-European Dialysis and Transplant Association; speakers bureau for AstraZeneca, Bayer, Boehringer, Esteve, FMC, Jansen, Mundipharma, Novo Nordisk, and Vifor; and serving as a member of Sociedad Catalana de Nefrologia. L. Zand reports receiving research funding from Genentech, Janssen Pharmaceuticals, and Mallinckrodt. All remaining authors have nothing to disclose.

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Dr. S.A. Bobart, Dr. A.S. De Vriese, and Dr. F.C. Fervenza designed the study; Dr. C. Andrades Gomez, Dr. S.A. Bobart, Dr. H. Han, Dr. J.C.L. Roman, and Dr. S. Tehranian collected the data; Dr. S. Tehranian analyzed the data and made the figures; Dr. C. Andrades Gomez, Dr. S.A. Bobart, Dr. A.S. Bombak, Dr. A.S. De Vriese, Dr. F.C. Fervenza, Dr. H. Han, Dr. J.C.L. Roman, Dr. S. Sethi, and Dr. L. Zand contributed to the analysis of the results and to the writing of the manuscript; and all authors revised the manuscript and approved the final version of the manuscript.

Supplemental Material

This article contains supplemental material online at http://cjASN.asnjournals.org/lookup/suppl/doi:10.2215/CJN.05480421/-/DCSupplemental.

Supplemental Figure 1. Patient flow at the Mayo Clinic.
Supplemental Figure 2. Patient flow at VHM.
Supplemental Figure 3. Patient flow at CUMC.

Supplemental Table 1. Characteristics of 101 patients with positive PLA2R antibodies and no evidence of associated disease or diabetes for the three cohorts.

Supplemental Table 2. Biopsy characteristics of 101 patients with positive PLA2R antibodies and no evidence of associated disease or diabetes for the three cohorts.

References


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