

Kidney Biopsy Is Required for Nephrotic Syndrome with PLA2R+ and Normal Kidney Function: The Con View

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KIDNEY360 1: 890–893, 2020. doi: <https://doi.org/10.34067/KID.0003262020>

The main obstacle to medical progress is dogma.

—Gabriel Richet

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adult patients of European decent (1,2). This morphologic pattern of injury is characterized by thickening of the glomerular capillary wall on light microscopy, presence of Igs (usually IgG and C3) deposition along the capillary walls on immunofluorescence microscopy, and subepithelial deposits along the glomerular basement membrane on electron microscopy (EM) (3). Primary MN, responsible for approximately 80% of cases, is a renal-limited autoimmune disease caused by circulating antibodies targeting antigens on the surface of the podocyte (4). The target antigen has been identified as the M-type phospholipase A2 receptor 1 (PLA2R) in 70%–80%, the thrombospondin type-1 domain containing 7A (THSD7A) in 1%–5%, and the recently described neural EGF-like 1 protein (NELL-1) in 5%–10% of cases (5–7). In approximately 20% of patients, MN is secondary to infections (hepatitis B), systemic autoimmune diseases (SLE), drugs (nonsteroidal anti-inflammatory drugs), or malignancy (8).

Traditionally, the gold standard for diagnosis of MN has been a kidney biopsy. However, the recent availability of assays for PLA2R has revolutionized the way we approach MN. There are two validated and commercially available assays for anti-PLA2R antibody: one is an ELISA, which provides a quantitative antibody titer and is 66.9% sensitive and 99.6% specific, and the other is a semiquantitative immunofluorescence assay test (IFA), which is 77.1% sensitive and 100% specific reported as positive, indeterminate, or negative. A large body of evidence supports a central role for serology in diagnosis and management of MN. The evidence is most explicit for PLA2R-associated MN, as this is the most common and longest recognized form. To start, the specificity of anti-PLA2R antibodies for a diagnosis of MN is close to 100% (9). Positive anti-PLA2R antibodies have not been found in patients with other kidney disease or healthy controls (1). Anti-PLA2R antibody titer correlates with clinical status (*i.e.*, disappearance of the antibody is associated with remission of proteinuria, whereas reappearance of the antibody may herald a relapse of proteinuria) (10–12).

Spontaneous remission is more likely in patients with low or moderate anti-PLA2R antibody titers (13,14), but it is rare in patients with high antibody levels (15). High levels of anti-PLA2R antibodies are associated with progression of proteinuria and declining kidney function over time (16,17). Changes in antibody levels precede changes in proteinuria, independent of the type of immunosuppressive treatment (12). Furthermore, serial measurement of anti-PLA2R antibodies levels may help in monitoring disease activity and response to immunosuppression (18).

As such, in 2017 we wrote a proposal for an individualized serologic-based approach to MN, aiming to complement and refine the traditional proteinuria-based approach to manage MN (19). We proposed that in a patient presenting with nephrotic syndrome, normal kidney function, positive anti-PLA2R antibodies, and no evidence for a secondary cause, a kidney biopsy was not needed because it was clear that the diagnosis was MN, and biopsy findings were unlikely to provide any information that would meaningfully change management. However, if a patient does not respond to immunosuppressive therapy or develops worsening kidney function, we submit that a renal biopsy should be performed.

We confirmed our hypothesis with a large cohort study in 2019. We reviewed all patients who had anti-PLA2R testing by simultaneous IFA and ELISA at the Mayo Clinic between January 2015 and June 2018. During this period, anti-PLA2R testing was performed in 838 unique patients, with positive results in 143 patients. In 132 of these patients, a native kidney biopsy was performed. The primary diagnosis in all biopsies was MN. Potential secondary causes were identified in 35 cases, most commonly malignancy and autoimmunity. Ninety-seven patients had a negative workup for secondary causes of MN. Sixty of these 97 patients had an eGFR > 60 ml/min per 1.73 m². In these patients, the kidney biopsy did not provide significant information that altered management. One patient had a superimposed diabetic nephropathy, pointing out that in a patient who is diabetic, a kidney biopsy is the only way to rule out underlying diabetic nephropathy, regardless of anti-PLA2R status. On the other hand, among the 37 patients with primary MN

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and $eGFR < 60$ ml/min per 1.73 m², additional findings included acute interstitial nephritis, diabetic nephropathy, and cellular crescents in one case each (20). These data confirmed our predictions that in patients with preserved kidney function and no evidence of secondary causes, a positive PLA2R antibody test (by both ELISA and IFA) highly predicts a tissue diagnosis of PLA2R-associated MN. We acknowledge that one drawback of this study is that not all centers may be able to perform both ELISA and IFA antibody testing. However, in this study, all patients with ELISA > 20 RU/ml had a diagnosis of membranous on biopsy. In a subgroup where ELISA was 2–20 RU/ml, the simultaneous use of IFA when positive confirmed a diagnosis of MN in this population. Thus, it is in this subgroup of patients with anti-PLA2R antibody levels between 2 and 20 RU/ml that simultaneous ELISA and IFA are more important to confirm the diagnosis of MN without a kidney biopsy.

We have now expanded our original observations by reviewing patients with positive serum PLA2R antibody tests by both ELISA and IFA performed from July 2018 to April 2020. A total of 1522 PLA2R tests were ordered on 1112 unique patients. Of these, 128 had a positive PLA2R antibody test, of which 95 were not included in our previous publication. We excluded those with allograft biopsy ($n=5$), those with no biopsy available ($n=18$), and pediatric patients ($n=2$). Of these 70 adult patients with positive PLA2R testing, the primary diagnosis in all biopsies was MN. Forty-two had a negative workup for secondary causes of MN. Thirty-two of the 42 patients (76%) had preserved renal function ($eGFR > 60$ ml/min per 1.73 m²). One patient had fibrin thrombi and neutrophils in one capillary loop that were not confirmed when reviewed by a second pathologist, blinded to the findings, and one patient had one glomerulus with focal glomerular basement membrane duplication. Neither of these findings altered diagnosis or management. Among the ten patients with $eGFR < 60$ ml/min per 1.73 m², additional findings that altered the treatment plan included acute interstitial nephritis ($n=1$) and superimposed diabetic nephropathy ($n=1$). Potential secondary causes were identified in 28 cases (autoimmunity =10, malignancy =6, nonsteroidal anti-inflammatory drugs =4, hepatitis =3, monoclonal protein =5) (20). Thus, we have now extended our previous observations to 92 patients with a positive PLA2R test by simultaneous ELISA and IFA, preserved renal function, and no evidence of secondary causes. In all of them, a kidney biopsy confirmed the diagnosis of MN and added nothing to the treatment approach.

Kidney biopsy is an invasive procedure. A meta-analysis of 34 studies that included 9474 biopsies found a rate of macroscopic hematuria of 3.5% and need for blood transfusion in 0.9% (21). Transfusion rates were higher for patients with a mean age of 40 years or older, which is well within the age range of patients with primary MN. A retrospective review of ultrasound-guided kidney biopsy done from January 1998 to December 2017 found an overall rate of complications of 16.6%, of which 1.5% were major (22). In addition, a review of all adult patients enrolled in the Boston Kidney Biopsy Cohort reported that major bleeding events occurred in 28 of 644 (4.3%) patients (28 required transfusion, four underwent angiographic intervention, and one had open surgery to control bleeding). We note that

there were higher complication rates when biopsies were performed in an urgent setting (23). Another study reported grade 3 hemorrhage in 64 of 18,947 (0.3%) procedures, including three deaths associated with the biopsy event (0.02% or approximately two of 10,000), with bleeding complications greatest in native kidney biopsies (24). Up to 24 hours postbiopsy, observation may be required, and techniques and capabilities vary among institutions. Furthermore, kidney biopsy is expensive. An estimated out-of-pocket cost for a patient without insurance in the United States is approximately \$10,000. To compound this, patients with severe nephrotic syndrome can present with thromboembolic complications, which necessitate the need for anticoagulation and often make renal biopsy even riskier. In a setting such as this, a sensitive and specific noninvasive diagnostic marker is extremely useful.

Arguing that a kidney biopsy is needed to evaluate chronic damage in a patient with $eGFR > 60$ ml/min per 1.73 m² is unfounded because renal function correlates well with total renal chronicity score (25,26). In our study, preserved renal function was associated with low total renal chronicity score, and although chronicity score increased as serum creatinine increased, it did not correlate with the degree of proteinuria (16). In the recent Membranous Nephropathy Trial Of Rituximab study, only four patients (3%) had a $> 20\%$ degree of tubular atrophy and interstitial fibrosis, and none of them had an $eGFR > 60$ ml/min per 1.73 m² (27). This further supports the view that a kidney biopsy does not provide information that cannot be derived from a routine serum creatinine level.

It may also be argued that knowledge of the degree of chronicity is useful when immunosuppressive therapy is considered. However, in our prior trials with rituximab (28,29), no correlation was found between the degree of interstitial fibrosis and response to therapy. This is consistent with observations that the degree of interstitial fibrosis and vascular scarring correlates more strongly with preexisting conditions, such as age, sex, and hypertension, than with absolute proteinuria in MN (26). Similarly, it may be argued that a renal biopsy may be helpful to estimate the duration of the membranous changes by the stages of deposits on EM. However, we would say that this information is irrelevant because the stage and heterogeneity of EM deposits do not correlate with any clinical variables at onset, nor do deposits predict rate of renal function decline or renal survival (26). Finally, we are not aware of any study showing that stages of deposits on EM correlate with response to therapy.

Some authors suggest that kidney biopsy could provide genetic and molecular data that could be useful to identify potential prognostic markers and new therapeutic agents (30), but these can be achieved with less invasive means. Genetic data can easily be obtained with a blood draw, and the best prognostic marker is induction of immunologic remission (*i.e.*, a negative anti-PLA2R antibody test) (31). However, patients who are anti-PLA2R negative by serum should undergo a kidney biopsy.

It is widely accepted not to biopsy children presenting with nephrotic syndrome because the likelihood that the diagnosis is minimal change disease is 80% (32). Similarly, a kidney biopsy is not required for the diagnosis of ANCA-associated vasculitis with renal involvement as demonstrated

in large Randomized Controlled Trials (33–36). Thus, it seems to be a *non sequitur* not to apply the same reasoning when the chance of getting a diagnosis right is almost 100%.

There have been recent anecdotal reports on internet forums, including the widely respected American Society of Nephrology communities, of patients with positive PLA2R antibodies by ELISA, and a renal biopsy did not show MN but most often, diabetic nephropathy. A closer look shows that the IFA was either negative or not performed. These cases highlight the importance of two things. (1) Both ELISA and IFA should be performed simultaneously to provide an additional layer of protection/confirmation. (2) In the presence of potential secondary causes of MN, diabetes as a cause of proteinuria, or eGFR <60ml/min per 1.73 m², a kidney biopsy is essential. Therefore, regardless of ELISA and IFA results, a kidney biopsy should be performed in patients who are diabetic with proteinuria.

Considering the Hippocratic words of “*Primum non nocere*,” a positive serum PLA2R antibody testing by ELISA, confirmed by IFA, is a useful and noninvasive method for the diagnosis of primary MN in the setting of preserved renal function and negative workup for secondary causes of nephrotic syndrome. This will spare the patient from an uncomfortable, time-consuming, and expensive procedure with the risk for major complication. However, if renal function is impaired or the patient has diabetes, a kidney biopsy allows exclusion of concomitant renal disease and may provide useful information to guide management.

Disclosures

All authors have nothing to disclose.

Funding

None.

Acknowledgments

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *Kidney360*. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions

S. Bobart was responsible for data curation, investigation, and validation; F. Fervenza conceptualized the study, provided supervision, data validation, and wrote the original draft; and S. Bobart and F. Fervenza reviewed and edited the manuscript.

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Received: May 22, 2020 **Accepted:** June 4, 2020

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