

Kidney Biopsy Is Required for Nephrotic Syndrome with PLA2R+ and Normal Kidney Function: Commentary

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Almost seven decades have elapsed since the paradigm-shifting description of percutaneous aspiration kidney biopsy was first published by Iversen and Brun (1,2). There is no doubt that this procedure has profoundly affected our understanding of kidney disease in general, and it has contributed greatly to improving medical care specifically in the field of glomerular diseases. But like all such advances, over time, new findings can alter the way in which the procedure is used and viewed. The concept of a potential “liquid biopsy” has emerged as an alternative to “tissue biopsy” with the development of sophisticated urinary proteomics and serum biomarkers of specific disease entities (3,4). Nevertheless, kidney biopsy continues to be the gold standard for diagnosis of underlying conditions when the clinical features are insufficiently distinct to provide a diagnosis and when additional information is needed to better guide prognosis and management. Although percutaneous kidney biopsy is generally regarded as safe when performed under ideal conditions by an experienced operator, major but usually nonlife-threatening complications can ensue in a small percentage of cases (5). Thus, the decision to pursue a strategy of kidney biopsy is governed by the risk of the procedure compared to the likelihood that the tissue will provide information that cannot otherwise be obtained noninvasively and that will make a difference in the management of the patient going forward. When the tissue is examined thoroughly by light, immunofluorescence, and electron microscopy, including special staining methods, kidney biopsies can often deliver a specific diagnosis and useful therapeutic guidance. These considerations form the crux of the proposition advanced in this debate, highlighted by the pro (6) and con (7) responses. Essentially, the debate asks whether positive results of testing for serum autoantibodies to PLA2R antigen in a well defined subset of adult patients presenting with nephrotic syndrome and normal kidney function will determine a diagnosis of a lesion of membranous nephropathy (MN) with such precision that the need for a kidney biopsy is obviated in a way that does not sacrifice vital information for aiding clinical therapeutics and prognostication. This is a challenging question and both the pro and con positions have elucidated crucial issues involved in its analysis. The central reference point is the study published by Bobart *et al.* (8).

This study was a retrospective, single-center analysis of the kidney biopsy findings in 132 patients with

a serum level of ≥ 2 RU/ml of anti-PLA2R antibody by a commercial ELISA (Euroimmun) confirmed by a positive indirect immunofluorescence assay (IFA; Euroimmun) on the same sample. Most, but not all, of the patients in this cohort had overt nephrotic syndrome. Importantly, 97 of these cases had no clinical evidence of a secondary cause by evaluation of antinuclear antibodies, antidouble-stranded DNA antibodies, hepatitis serology, chest x-rays, age-appropriate cancer screening, medication history, and mAb testing. The presence of diabetes mellitus was not a specific reason for exclusion from this cohort. Of these 97 patients, 60 (62%) had a “normal” eGFR arbitrarily defined as >60 ml/min per 1.73 m², not adapted to the age of the patients (which had an interquartile range of 44–60 years). An eGFR of <45 ml/min per 1.73 m² was present in 22 out of 97 patients. The median proteinuria was 8.0 g per day and the median serum albumin level was 2.7 g/dl (by the bromocresol green method). The crucial finding was that among the 60 patients with a normal eGFR, 100% had a lesion of MN. One patient had superimposed diabetic nephropathy and one patient had a superimposed lesion of focal and segmental glomerulosclerosis. No features of secondary MN were found in any of the biopsy specimens. PLA2R antigen staining of glomeruli was pursued in 52 of these 97 patients, and was positive in 51 (98%). Thus, the diagnosis of presumed primary (PLA2R-mediated) MN could be obtained with 100% specificity (no false positives) in patients meeting the definition of a positive anti-PLA2R antibody used in this study (a combination of ELISA and IFA test results), who had normal kidney function and no evidence for a secondary form of MN. Also, in this cohort, the ability to stain glomeruli for PLA2R antigen added little to diagnostic accuracy. These findings meet the criteria for a liquid biopsy. According to the authors, the findings in kidney biopsy in this cohort provided no additional information useful for prognostication or therapeutic decision making, but no follow-up is provided for verification of this statement. On the other hand, kidney biopsy in the 37 of 97 (38%) patients meeting all of the definitions but having reduced eGFR resulted in additional diagnostic information in five patients. As this subgroup is not the subject of this debate, they need no further discussion. In the con discussion, the authors (7) add another 42 cases meeting the definitions described above

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(bringing the total studied between January 2015 and April 2020 to a total of 139 cases). MN was present in 42 out of 42 patients (100%, no false positives), confirming the earlier published studies. These findings are quite similar to those using the Western blot technique for identifying anti-PLA2R antibodies described in the classic and seminal description of PLA2R-mediated MN by Beck Jr. *et al.* (9).

The pro position in this debate taken by Hogan (6) contains three main elements, specifically (1) it is premature to make a change in practice on the basis of a single retrospective study from one institution, (2) the optimum criteria for a “positive” anti-PLA2R antibody test are not well understood, and (3) to what population of patients does the paradigm of liquid biopsy apply? The outline of data needed to further validate the Bobart *et al.* (8) paradigm/algorithm is quite reasonable.

The original authors fully agree with statement 1: “Further validation in a prospective study is warranted to determine whether PLA2R antibody testing be used as a non-invasive diagnostic test to guide therapy” concludes the Abstract portion of the paper (8). Further, they postulate that the evidence provided might help in biopsy decision making in patients with a high risk of complications (*e.g.* coagulation defects, inability to cooperate with the requirements of the procedure, such as breath holding) or situations where the procedure might be relatively contraindicated (*e.g.* single kidney). Clearly, the presence of abnormal kidney function will nearly always justify a kidney biopsy even with a positive anti-PLA2R antibody testing. Whether the definition of abnormal kidney function needs to be age-adapted is a question for future studies.

The optimum criteria for defining a positive PLA2R antibody test has been clearly identified by the original paper of Bobart *et al.* (8). Both the ELISA and the IFA tests are required, preferably performed on the same sample of serum. A negative IFA does not require a confirmatory ELISA, but a positive IFA test requires confirmation by an ELISA ≥ 2 RU/ml (see the algorithm in Bobart *et al.*) (8).

False-positive ELISA assays (ELISA > 20 RU/ml with a non-MN lesion by kidney biopsy) have been described (largely anecdotally), but not systematically studied. This phenomenon seems to be more common in patients with diabetic nephropathy, for unexplained reasons. The IFA is usually negative in such circumstances, and thus would not qualify as a positive test, according to the Bobart *et al.* criteria (7,8). At the 2020 European Renal Association-European Dialysis and Transplant Association virtual meeting, an Abstract was presented by Mok and Choo describing 31 patients with non-MN lesions on kidney biopsy who had positive ELISA anti-PLA2R tests, 26 of whom had levels < 50 RU/ml and five of whom had levels > 50 RU/ml (ranging from 56 to 168 RU/ml). All of the patients were Chinese or Indian. No IFA results were reported, so this study cannot be interpreted in relationship to the Bobart *et al.* criteria (7,8). However, this single study validates the need to study additional ancestral populations beyond those included in the original Mayo Clinic study (8). The results described in the positive anti-PLA2R patients in the Bobart *et al.* study (8) presenting with nephrotic syndrome and potential secondary causes of MN, or systemic diseases such as diabetes, or an eGFR < 60 ml/min per 1.73 m², demand that a kidney biopsy be undertaken as clearly stated in the con position (7,8), and I agree.

Although the data provided in the Bobart *et al.* (8) cohort study are very compelling concerning the utility of anti-PLA2R serology (both ELISA and IFA) for noninvasive diagnosis of suspected MN in patients presenting with nephrotic syndrome in the absence of reduced renal function and evidence of a secondary cause, an unresolved question remains. Does the absence of morphologic data concerning variations in the MN lesion impair or constrain therapeutic decision making and/or prognostication? We can be reassured by the authors claims that the answer to this question is no, at least in the cohort described (7,8), but more detailed and longer-term follow-up would help to assuage doubts. Presently, serial determinations of anti-PLA2R serology (mainly ELISA) *via* quantitative urinary protein excretion and serum creatinine levels seem to be sufficient for management purposes.

After due consideration of both the pro and con positions, my own conclusions are more supportive of the con position, so long as the definition of PLA2R seropositivity conforms to the Bobart *et al.* criteria (8), the eGFR is normal (for age), and secondary causes seem unlikely on the basis of a standardized evaluation. However, in concurrence with the pro position and the authors of the original paper, this newly proposed paradigm needs independent confirmation by a prospective study involving individual patients of diverse ancestry.

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Author Contributions

R. Glasscock conceptualized the study, was responsible for data curation and formal analysis, wrote the original draft, and reviewed and edited the manuscript.

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See related debates, “Kidney Biopsy Is Required for Nephrotic Syndrome with PLA2R1 and Normal Kidney Function: Pro” and “Kidney Biopsy Is Required for Nephrotic Syndrome with PLA2R1 and Normal Kidney Function: The Con View” on pages 887–889 and 890–893, respectively.