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Review

Clinical usefulness of autoantibodies to M-type phospholipase A2 receptor (PLA2R) for monitoring disease activity in idiopathic membranous nephropathy (IMN)

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ABSTRACT

Autoantibodies to M-type phospholipase A2 receptor (PLA2R) are specific markers of idiopathic membranous nephropathy (IMN). They can differentiate IMN from other glomerular diseases and primary from secondary forms of MN. Preliminary data suggest that anti-PLA2R antibody titer correlates with disease activity but more solid evidence is needed.

To evaluate the performance of anti-PLA2R antibody for monitoring nephropathy activity, 149 anti-PLA2R antibody measurements were performed during the follow-up of 42 biopsy proven IMN consecutive patients. Patients were enrolled either at time of diagnosis (33 cases, inception cohort) or after diagnosis (9 patients, non-inception cohort).

Anti-PLA2R detection was performed using the highly sensitive transfected cell-based indirect immunofluorescence (IIFT).

Over the follow-up there was a linear time–trend of decreasing proteinuria ($P < 0.001$), increasing serum albumin ($P < 0.001$) and decreasing PLA2R antibody levels ($P = 0.002$). There was a statistically significant association between changes in PLA2R antibody levels and the clinical course of PLA2R-positive IMN. The positive PLA2R serum antibody status was linearly associated with increasing proteinuria and decreasing serum albumin over time, compared with negative antibody status. Moreover, the strong correlation between the clinical conditions and PLA2R antibody levels allowed the prediction of prevalence distribution of patients with active disease, partial and complete remission. Over the course of the follow-up, the probability of halving proteinuria increased 6.5 times after disappearance of PLA2R antibodies.

Our data suggest that the serial evaluation of anti-PLA2R antibodies could help in optimal timing and duration of the immunosuppressive therapy, reducing over(under)-treatment and associated side-effects.

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Contents

1. Introduction

Membranous nephropathy (MN), an autoimmune glomerular disease, is the main cause of nephrotic syndrome in adults. It is mostly idiopathic, but in up to 20–30% of cases it is secondary to different pathological conditions such as systemic rheumatologic diseases, infections, toxics or drug exposure and malignancies [1,2]. MN may be slowly progressive or may spontaneously go into remission, but over the years up to 30–40% of patients progress to end stage renal disease.

Sub-epithelial immune deposits and complement activation, alterations in podocyte structure, functional impairment of the glomerular capillary wall with altered filtration barrier and proteinuria characterize MN.

Neither specific diagnostic biomarkers nor reliable predictors for the spontaneous course of the disease and/or predictors for the need and intensity of immunosuppressive treatment were available lately [3].

Although the immunological pathogenesis of MN was established more than 50 years ago [4,5], the specific target(s) of the autoimmune response in humans was(were) undiscovered until recently, when the preeminent role for autoantibodies recognizing podocyte antigens has been suggested [6,7,8,9,10].

The M-type phospholipase A2 receptor (PLA2R) was recently identified as the major target antigen in adult idiopathic MN (IMN) [11,12,13,14], being circulating antibodies against PLA2R found in about 70% of the patients, but only very rarely in secondary MN and in other glomerular diseases [11,15,16,17,18].

Moreover, the strong association of the PLA2R1 gene with IMN in a recent genome-wide association study suggests that some genetic variants of PLA2R1 are at risk for the disease [19,20,21,22].

Preliminary data suggest that anti-PLA2R antibody levels correlate with clinical activity as measured by proteinuria, and change in autoantibody titer would precede change in proteinuria [23,24]. Anti-PLA2R antibody titer would therefore be predictive for the outcome [17,25] and response to treatment [26]. The last point, if confirmed, would allow a therapeutic strategy tailored on the single patient, an effective way of limiting patient exposure to toxic drugs, without reducing the efficacy of treatment, while reducing the costs. Finally, anti-PLA2R autoantibodies were reported as useful to estimate the risk of MN recurrence after kidney transplantation [27,28,29,30].

Whereas the diagnostic significance of anti-PLA2R antibodies has been confirmed in several reports [31], only a few studies have examined the longitudinal (i.e., repeated measures) relation between the clinical picture of MN and the level of PLA2R antibody. In the present retrospective study, by taking advantage of the centralized assessment of PLA2R antibody at our laboratory from different Nephrology Units across Italy, we examined the association between changes in PLA2R antibody levels and the clinical course of PLA2R-positive MN, using a longitudinal design and analysis.

2. Material and methods

2.1. Study population

2.1.1. Inclusion criteria

All consecutive patients with histological diagnosis of MN and positive PLA2R Abs in the serum identified between 24.03.11 and 17.06.14 were included. Patient serum samples were collected at the Institutions where the patients were diagnosed and followed. Samples were collected, processed and tested immediately or frozen at −20 °C until testing. The diagnosis of idiopathic MN and the clinical evaluation of the disease activity were done by the physician in charge for the study in each of the participant Nephrology Units.

As routine clinical practice, the Laboratory requests that the Clinical Center, which sends the sample for PLA2R Abs determination, also included clinical data on ad hoc pre-printed data sheet. The Laboratory also recommends that the physician in charge for the patient care re-assesses PLA2R Abs status at most at 3, 6 and 12 months, and then yearly, after the initial determination, unless there was a new clinical indication. Given that the recommendations allowed the physicians a certain degree of flexibility, time points of PLA2R Abs differed across different patients.

We distinguished between patients enrolled at time of diagnosis (Inception Cohort), or after diagnosis (Non-inception Cohort).

The study was approved by the local Ethics Committee (N. 150/ST/2014, 01.10.2014) and informed consent was obtained for all participating patients for the treatment of data already collected for routine clinical use. Patient data were anonymously used under consideration of the latest version of the Helsinki Declaration of Human Research Ethics.

2.2. Medical history

There is no specific universally accepted treatment for membranous nephropathy; therefore, some of the patients included in the study were on supportive care, that means they received only symptomatic drugs such as angiotensin-converting enzyme inhibitors in combination or not with angiotensin II receptor blockers, diuretics and albumin/plasma expanders, while the others received different kinds of immunosuppressive schemes.

Immunosuppressive treatment options included the use of corticosteroids, alkylating agents, cyclosporin A or other calcineurin-inhibitors, mycophenolate/mofetil and rituximab, but their use is