Port J Nephrol Hypert 2015; 29(3): 266-268
Advance Access publication 31 July 2015

Meneses G, Viana H, Santos MC, *et al.* Antiphospholipase A2 receptor antibodies in the diagnosis of idiopathic membranous nephropathy. *Port J Nephrol Hypert* 2015;29:44-47.

Does idiopathic imply autoimmune causation in membranous nephropathy? A new twist in the aetiopathogenesis of the disease

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Membranous nephropathy (MN) is the most common glomerulopathy underlying idiopathic nephrotic syndrome (INS) in adults and elderly, especially in Caucasian populations[1-3]. However, during the recent past, a declining trend has been observed in the incidence of MN and in many areas, focal segmental glomerulosclerosis (FSGS) has taken over as the leading cause of INS, particularly in adults and non-Caucasians[4-6]. Despite this trend, MN still remains the commonest cause of INS in adults and elderly worldwide. Its clinical course is highly varied. It leads to end-stage renal disease (ESRD) in about one-third of patients[7-10]. This, coupled with its widespread prevalence in many countries, has led to MN being one of the most common causes of ESRD and a frequent indication for kidney transplantation in many western countries[11]. We found a prevalence of MN of 26.6 % in 316 adult patients with NS in a study in which FSGS was the predominant pathological lesion (39.8%)[6].

Aetiologically, MN has been divided into primary or idiopathic and secondary forms[1,2]. The later may be caused by a variety of insults to the kidney, including infections, tumours, autoimmune diseases, drugs, etc[2]. If no cause is found after extensive clinical and laboratory evaluation, then MN is designated as idiopathic MN (iMN). Thus, iMN was basically a diagnosis of exclusion of all known causes associated with MN and no specific marker was available to classify MN till recent past. However, this idiopathic puzzle has recently been disentangled. A number of investigators have found the culprit antigens predisposing to antigen antibody complexes[12-15]. The iMN is now considered to be an autoimmune disease resulting from the production of anti-phospholipase A2 receptor (PLA2R) antibodies and anti-PLA2R antibodies are being used as specific biomarkers for the iMN diagnosis[16].

Meneses *et al.* have investigated the prevalence, sensitivity and specificity of anti-PLA2R antibodies in the sera of 38 patients with iMN (n = 33) and secondary MN (n = 5) from a single centre in Portugal[16]. The sensitivity of the test was 57.5% while the specificity was 100%. The authors utilized both the immunoflourescence and enzyme linked immunosorbent (ELISA) assays for the demonstration of circulating antibodies. Previous reports have shown a prevalence of 70 to 80% of anti-PLA2R in iMN. The low sensitivity of the test in this particular cohort may be due to the small number of patients. In

addition, the vast majority of patients who tested negative (71.4%) were in either partial or complete remission. It has been claimed that during remission the titers of the antibody become undetectable. The authors thus concluded that prior treatment seems to decrease the prevalence of the antibodies and lower the sensitivity of the test. The test was also negative in patients with lupus MN, implying that lupus MN is not pathogenetically related to iMN. A number of other investigators have also explored the diagnostic utility of this test and found it to be a reliable marker of iMN diagnosis[17-20]. The specificity of the test has also been validated in numerous studies[17-20]. A number of workers have also tested the presence of PLA2R antigen at the tissue level with overall good correlation between the serum antibody levels and the tissue deposits of the antigen. There are, however, still many questions regarding the assays used for measuring the circulating anti-PLA2R antibodies that remain to be answered and the discovery of answers to these questions may help in realizing the dream of personalized diagnosis and treatment of MN very soon[21,22].

The circulating anti-PLA2R antibodies also provide crucial information about the activity of the disease, thus helping in monitoring the disease. The titers of antibodies can be monitored during treatment of the disease. Measurement of anti-PLA2R antibodies at the end of immunosuppressive therapy has been shown to predict the subsequent course of the disease[14,22].

Meneses *et al.* have suggested large-cohort prospective studies integrating the degree of proteinuria, immunosuppressive treatment, time of testing, serial measurements of anti-PLA2R levels and glomerular deposits of anti-PLA2R for clarifying the missing links in the unfolding story of iMN pathogenesis and pathology[16,21]. We hope that the authors will continue their research work in this area and try to find answers to the above and other relevant questions in this arena of active research in nephrology. With the development of new generation, more robust assays for detecting these antibodies, it may be possible to diagnose the disease, monitor its activity and treatment, without recourse to the invasive renal biopsy.

In conclusion, the discovery of PLA2R as the target antigen of iMN and the development of assays for the detection of circulating antibodies against this antigen has paved the way for a better understanding of the pathogenesis of MN and this may ultimately lead to personalized therapy of the patients with this disease.

Conflict of interest statement: None declared.

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