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Phospholipase A2 receptor (PLA2R) related membranous nephropathy - not specific for idiopathic cases any more

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ABSTRACT

Context: Membranous nephropathy is among the most common causes of nephrotic syndrome in adults.

Evidence Acquisitions: PubMed, EBSCO, Web of Science, directory of open access journals (DOAJ), EMBASE, and Google Scholar with keywords of phospholipase A2 receptor, PLA2R, membranous nephropathy, nephrotic syndrome, idiopathic nephrotic syndrome and glomerulonephritis have been searched.

Results: The recent finding that around 70%-80% of the idiopathic cases of membranous nephropathy express Phospholipase A2 receptor (PLA2R) in their kidney biopsies and anti-PLA2R antibody in their serum was initially considered specific to the idiopathic cases. However, more recent studies have shown that while PLA2R glycoprotein expression, and anti-PLA2R antibodies, are specific to membranous nephropathy and are not seen in other glomerulonephritides, they can be as frequently expressed in certain secondary forms of membranous nephropathy.

Conclusions: In this communication we intend to briefly review the new data regarding tissue and sero-positivity for PLA2R in different types of secondary membranous nephropathy, as well as pathologic and immunofluorescence features of them as compared to the idiopathic cases.

Short-Review

Implication for health policy/practice/research/medical education:
To clarify the value of checking PLA2R serology and tissue staining in cases of membranous nephropathy, and its lack of specificity in distinguishing idiopathic versus some secondary cases.

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1. Context

Membranous nephropathy (MN) is among the most common primary glomerulopathies in adults. It accounts for 20% of cases of idiopathic nephrotic syndrome in adults, leads to end stage renal disease (ESRD) in up to one-third of the patients, and is the leading glomerulopathy recurring after kidney transplantation (1,2).

Sub-epithelial immune complexes of IgG and membrane attack complex of complement system cause thickening of glomerular capillary walls with little or no cellular proliferation or infiltration in the glomeruli, leading to proteinuria and nephrotic syndrome. While MN can be secondary to hepatitis B, hepatitis C, autoimmune diseases, thyroiditis, malignancies, sarcoidosis, and certain drugs such as gold, captopril, penicillamine, and non-steroidal anti-inflammatory drugs, in the majority (70%-80%) of cases none of these etiologies can be found, and thus are labeled as "primary" or "idiopathic" MN.

2. Evidence Acquisitions

PubMed, EBSCO, Web of Science, directory of open access journals (DOAJ), EMBASE, Scopus and Google Scholar with keywords of phospholipase A2 receptor, PLA2R, membranous nephropathy, nephrotic syndrome,

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idiopathic nephrotic syndrome and glomerulonephritis have been searched.

3. Results

A major recent breakthrough was the identification of a podocyte glycoprotein antigen, the M-type phospholipase A2 receptor (PLA2R) as the major target antigen for circulating autoantibodies in about 70% of cases of primary (idiopathic) MN, resulting in in-situ formation of immune complexes in the sub-epithelial space of glomerular capillaries (3,4). This confirmed the hypothesis that most cases of primary (idiopathic) MN are the result of an autoimmune antibody response targeting podocyte PLA2R antigen (4). Moreover, while patients with idiopathic MN who have circulating anti-PLA2R antibodies would all show a strong PLA2R staining in their kidney biopsies (5-7), none of those who are tissue PLA2R stain negative have circulating antibodies to PLA2R. Also, 24 of 33 patients (73%) with idiopathic MN whose renal biopsies were positive for PLA2R had circulating anti-PLA2R antibodies, while nine (27%) were serum negative. Of the seventeen patients with idiopathic MN who had no circulating antibody to PLA2R, nine patients (53%) had positive tissue staining for PLA2R suggesting that renal PLA2R positivity is associated with the production of serum PLA2R autoantibodies, and thus reflecting disease activity and severity (Tables 1 and 2). Furthermore, multiple reports have shown that serum anti-PLA2R antibody titer is associated with disease activity and severity, and long-term outcomes (4,5,8,9). Decline in anti-PLA2R antibody titer in response to immunosuppressive therapy with rituximab (a monoclonal antibody against CD-20 cell surface antigen of B lymphocytes) precedes the clinical response of a decline in proteinuria by few to several months (10,11). Multiple studies have shown that circulating PLA2R antibodies and tissue PLA2R staining are specific to cases of MN and not to any other type of primary glomerulonephritis (4-6,12). Positive serology for anti-PLA2R antibodies has been shown to have a sensitivity of 70%-82% and specificity of 89%-100% for detecting idiopathic MN (4,12). Furthermore, in a report of 165 cases of MN, including 85 idiopathic and 80 secondary MN cases, they found a positive tissue staining for PLA2R to have a sensitivity of 75% and specificity of 83% for idiopathic MN (13). However, contrary to the initial impression that PLA2R was specific to cases of idiopathic MN, it is now clear that it can be seen in cases of secondary MN of diverse etiologies (13). In that report, among 165 cases of MN, PLA2R positive staining was found in 64 of 85 (75%) idiopathic MN cases, 7 of 11 (64%) hepatitis C associated MN, 3 of 4 (75%) sarcoidosis associated MN, and 3 of 12 (25%) neoplasm associated MN cases (13). Among 46 cases of MN secondary to autoimmune etiologies (e.g., SLE, Sjogren's, RA, MCTD, ANCA) only 1 (2%) showed PLA2R positive staining (13) (Table 3).

Morphological features commonly associated with secondary MN include presence of mesangial deposits, segmental involvement of glomeruli by deposits, and "full house" immunofluorescence staining. However, among the 78 PLA2R-positive cases, there was only a slightly higher percentage of secondary MN cases with mesangial deposits (43%) than idiopathic MN (30%) cases, statistically not significant (13). Thus, presence of mesangial deposits in PLA2R-positive cases is not a useful marker to separate idiopathic from secondary MN cases (13). However, "full house" immunofluorescence stain and sub-endothelial deposits were highly specific for secondary MN, as all cases with these findings had a known primary etiology and were PLA2R negative (13). Another important finding was that while IgG4-predominant staining is a feature of idiopathic MN (whereas IgG1 IgG2, and IgG3 are more prominent in secondary MN cases), in cases of PLA2R positive secondary MN due to hepatitis C, sarcoidosis or

Table 1. Correlation between tissue staining for PLA2R and serum anti-PLA2R antibody status in cases of idiopathic MN

	Serum +	Serum -
Tissue +	73%	27%
Tissue -	0%	100%

Table 2. Correlation between serum anti-PLA2R antibody status and tissue staining for PLA2R in cases of idiopathic MN

	Tissue +	Tissue -
Serum +	100%	0%
Serum -	53%	47%

Table 3. Tissue PLA2R or serum anti- PLA2R positivity in different types of glomerulonephritides

	Tissue +	Serum +
GNs other than MN (4-6,12)		0%
Autoimmune disorders – MN (SLE, Sjogren's, RA, MCTD, ANCA) (13)	2%	
SLE- class 5 GN (5)	2.6%	
Idiopathic MN (3-5, 12,13)	75-84%	70-82%
Hepatitis C – MN (13)	64%	
Hepatitis B – MN (5)	64%	
Sarcoidosis – MN (13 ,14)	61.5%	
Malignancy – MN (13)	25%	

Abbreviations: GN, glomerulonephritis; MN, membranous nephropathy; SLE, systemic lupus nephritis; RA, rheumatoid arthritis; MCTD, mixed connective tissue disease; ANCA, anti-nuclear cytoplasmic antibody.

neoplasm, IgG4 was the predominant IgG suggesting that these cases were more similar to idiopathic than other secondary MN cases (13). Interestingly, IgG subtype analysis of PLA2R negative idiopathic MN cases showed that 7 out of 17 such cases did not show IgG4 dominance, suggesting that some of them could have been undetected secondary MN cases (13).

In another report, of 102 cases of idiopathic MN 86 (84%) cases, and of 39 cases with hepatitis B associated MN 25 (64%) cases showed renal tissue staining for PLA2R(5). This was in sharp contrast to only 1 out of 38 cases of SLE-class 5-GN showing PLA2R staining (5) (Table 3). Interestingly, there was no significant difference between the intensity of PLA2R staining in the positive cases of hepatitis B associated MN and idiopathic MN (5). Moreover, co-localization studies showed that renal PLA2R staining overlapped with HBsAg, HBcAg, and HBeAg along the glomerular capillary loops (5). In the hepatitis B associated MN patients, PLA2R positive biopsies showed stronger IgG, and weaker C1Q and C4 staining that PLA2R negative biopsies. Also, the degree of IgA and IgM immunofluorescence staining, and mesangial electron dense deposits were significantly higher in hepatitis B associated MN than idiopathic MN patients, suggesting the secondary nature of hepatitis B associated MN (5). There were no differences in the degree of IgG and C3 staining, and sub-epithelial electron dense deposits between PLA2R positive idiopathic MN and hepatitis B associated MN cases (5). Moreover, PLA2R exhibited a granular immunofluorescence staining along the glomerular capillary loops that co-localized with HBsAg suggesting that the hepatitis B virus might have caused podocyte damage leading to over expression or change in antigenicity, or conformational changes in PLA2R in glomerular capillary loops. These findings suggest that hepatitis B associated secondary MN is a PLA2R associated disease.

In a report of 26 patients with sarcoidosis and glomerular disease, 11 patients had MN, out of 9 cases studied 5 (55%) cases, and all 5 patients with active sarcoidosis at the time of kidney biopsy had PLA2R antigen in their immune deposits, while none of those with inactive sarcoidosis had detectable PLA2R (14) (Table 3). Interestingly, in 2 patients with available follow up sera, anti-PLA2R antibody levels followed sarcoidosis disease activity (14). This was surprising since sarcoidosis results from an uncontrolled cell-mediated immune response involving macrophages and Th1 cells (15) after exposure to an unidentified antigen, whereas MN is an autoimmune antibody response involving Th2 cells and B-lymphocytes (16,17).

The above reports indicate that PLA2R sero-positivity and/or tissue staining is not specific to cases of idiopathic MN and can be as prevalent in some cases of secondary MN, e.g., hepatitis B, hepatitis C, neoplasms, and sarcoidosis associated MN (5,12-14) (Table 3). In such cases, whether idiopathic MN or secondary MN, renal podocyte damage may lead to over expression or conformational change in the glycoprotein PLA2R that makes it more immunogenic and thus a positive tissue staining and a positive serology. It has also been suggested that polymorphisms of PLA2R and HLA complex class II (HLA-DQA1) are associated with idiopathic MN, but their effect on renal PLA2R and anti-PLA2R antibody production remain unclear (18,19). Also, the potential effects of these polymorphisms on secondary MNs that are associated with high prevalence of PLA2R expression in kidney tissue and/or positive serology has not been investigated.

Conclusions

In summary, while the recent findings of PLA2R presence in a majority of cases of idiopathic MN were promising and it distinguished them from all other glomerulonephritides, the new reports show that it can be found in a number of secondary cases of MN as well.

Author's contribution

BB was the single author of the manuscript.

Conflicts of interest

The author declares no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the author.

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