Triggers, Bullets and Targets, Puzzle of Membranous Nephropathy

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ARTICLE INFO

Article type:
Review Article

Article history:
Received: 16 Sep 2011
Revised: 13 Oct 2011
Accepted: 25 Oct 2011

Keywords:
Glomerulonephritis, Membranous
Phospholipase A2
Rituximab
6B1 IgG4 Monoclonal Antibody

1. Introduction

Idiopathic Membranous Nephropathy (iMN) is a common cause of adult nephrotic syndrome. For more than 50 years researchers have debated for an autoimmune basis of MN, but the auto-antigen remained elusive (1). In 2009, Beck and colleagues discovered that autoantigen is mainly a M-type trans-membrane phospholipase A2 receptor (PLA2-R) located on podocytes, and autoantibody is mainly a non-complement fixing- IgG4 (1). With these new findings iMN should no longer be considered as an idiopathic disease. Very recently a new indirect immunofluorescence test (IIFT) enabled early detection of anti-PLA 2 R antibody in the serum of patients with iMN by which anti-PLA 2 R antibodies were found in 52% of patients with biopsy-proven iMN (2). However, the triggers of autoantibody production and mechanisms of its action are yet unknown and investigations for other likely antigens are in progress (3, 4).

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DOI: 10.5812/numonthly.2330
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2. Materials and Methods

In this mini review, the author searched the MEDLINE as at initiation of ideas about Rituximab treatment and M-type phospholipase A2 receptor autoantibody in iMN up to October 2011. All English-language studies that reported diagnosis and treatment of idiopathic MN were searched using the terms “membranous nephropathy”, “rituximab” and, “phospholipase A2 receptor”. We included important studies by cross-referencing. We also included author’s definitions of some conditions such as complete remission (CR) and partial remission (PR) in our review.

3. Results and Discussion

3.1. Anti-Phospholipase A2-Receptor Antibodies

In its early discovery by Beck and colleagues, using Western blot assay 26 out of 37 (70%) serum samples of American patients with iMN showed an antibody (mainly IgG4) against a 185-kD PLA2-R glycoprotein in the glomerular extract (1). In a report from China, by the use of a Western blot assay, 49 out of 60 patients (82%) with idiopathic MN demonstrated detectable anti-PLA2-R auto-antibodies (5).

In an European cohort of iMN patients, they measured anti-PLA-R auto-antibody levels by a Western blot assay, 26 out of 37 (70%) serum samples of American patients with iMN showed an antibody (mainly IgG4) against a 185-kD PLA2-R glycoprotein in the glomerular extract (1). In a report from China, by the use of a Western blot assay, 49 out of 60 patients (82%) with idiopathic MN demonstrated detectable anti-PLA2-R auto-antibodies (5).

In an European cohort of iMN patients, they measured anti-PLA-R auto-antibody levels by a Western blot immunoassay in serum samples of patients in nephritic proteinuria, remission, or relapse periods. Fourteen out of 18 (77.8%) patients showed IgG4 auto-antibody in their active phases; it was decreased significantly during remission and increased again during relapse (6). In a recent report, PLA2-R autoantibody was found in 5 out of 10 patients with recurrent iMN but in none of 9 patients with de novo MN following renal transplantation (7).

3.2. Antigen Targets

The super-family of phospholipase A2 (PLA2) consists of distinct types of structurally related enzymes (8). Family of secreted PLA2s (sPLA2) by itself has a widespread distribution in nature and presents in different fluids and tissues as an antibacterial protection (9, 10). PLA2-Ia is found in snake venom and other serpent’s maxillary glands (11). High-molecular weight cytosolic PLA2 (cPLA2) is located on the cell membrane or endoplasmic reticulum and acts as an intracellular second messenger. There is an intensive relationship between cPLA2 and sPLA2. PLA2-R is expressed not only in human kidney but also in lung, pancreas, placenta, and skeletal muscle (13).

Inflammatory cytokines such as IL-6, TNF-α, and IL-β induce the synthesis and release of sPLA2 from different cells (13). Mammalian sPLA2 could attach to PLA2-R and induce pro-inflammatory signals by a receptor-mediated mechanism. Heymann nephritis (HN) is an experimental rat model of Nephrotic syndrome (NS), but Megalin, the auto-antigen of HN does not express on human podocytes. Epithelial cell injury in Heymann nephritis is induced by complement C5b-9 deposition, and sub-lytic injury to podocytes, activate finally cPLA2, an important mediator of podocyte injury and actin cytoskeleton collapse, through increasing intracellular calcium and protein kinase C (PKC) activation, and extracellular signal-regulated kinase (ERK) (3, 14). IgG4 is unique among IgG subclasses because it weakly activates the complement. Whether IgG4-PLA2-R interaction in human is similar to sub-lytic C5b-9 induced podocyte injury in Heymann nephritis and what the triggers are for anti-PLA2-R production still remain unknown.

PLA2-R has been discussed as the major candidate antigen of idiopathic MN (Tablet and Figure 1). The nature of antigens involved in remaining cases of idiopathic MN is unclear. In a very rare form of neonatal nephritic syndrome, neutral endopeptidase (NEP) deficient mother may develop antibody against NEP during conception and transmit the antibody during next pregnancy to subsequent fetus. Transmitted antibody is mainly IgG1. Notably, when the transmitted antibody is non-complement fixing IgG4, membranous nephropathy is not developed in the child (15, 16).

Antibody against aldose reductase (AR) and manganese superoxide dismutase (SOD2) have been detected in Table 1. Target Antigens, Antibodies, and Possible Triggers in Idiopathic MN

| Target Antigen       | Antibody                                      | Trigger                                      | Presentation          |
|----------------------|-----------------------------------------------|----------------------------------------------|-----------------------|
| NEP<sup>a</sup>      | Anti-NEP antibody both IgG4 and IgG1, disease is not developing if the transmitted antibody from mother is a non-complement fixing IgG4 subclass | NEP deficiency | Neonatal iMN<sup>a</sup> |
| PLA2-R<sup>b</sup>   | Anti PLA2-R antibody mainly a non-complement fixing IgG4 antibody | Unknown | iMN |
| AR/SOD2              | Anti-AR and anti-SOD2 IgG4 antibody with C5b-9 deposition (6) | These antigens are exposed after primary injury | iMN |
| BSA<sup>c</sup>      | Anti-BSA, mainly IgG4 and IgG1 formation with C5b-9 Deposition | Undigested BSA enters the circulation | IMN (Childhood) |

Abbreviations: AR: Aldose reductase; BSA, cationic bovine serum albumin; iMN, idiopathic membranous nephropathy; NEP, neutral endopeptidase; PLA2-R, M-type phospholipase A2 receptor; SOD2, manganese superoxide dismutase
<sup>a</sup>NEP deficient mother may develop antibody against NEP during conception.
<sup>b</sup>PLA2-R, a trans-membrane protein located on podocytes
<sup>c</sup>Cationic bovine serum albumin binds to anionic glomerular capillary wall.
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Figure 1. IgG4 Antibody Against M-type Phospholipase A2 Receptor (PLA2-R) Is the Main Antibody in Pathogenesis of Idiopathic Membranous Nephropathy. Antibodies to aldose reductase (AR) and manganese superoxide dismutase (SOD2) may work as the second hit after primary anti-PLA2-R antibody injury. Anti-neutralendopeptidase (NEP) has been reported in rare instances of neonatal MN, and antibody against cationic bovine serum albumin (BSA) has been reported in a small group of children with idiopathic MN.

3.3. Treatment

Spontaneous remission (not induced by immunosuppressive therapy) is a well-known characteristic of iMN; its incidence ranges from 30% to 50% and carries a favorable outcome. Conservative therapy has been recommended for all patients with iMN and if proteinuria is decreased more than fifty percent (>50%) of baseline during the first year of follow-up, it predicts the appearance of spontaneous remission. Immunosuppressive therapy should be considered without delay for patients with deteriorating renal function and for those without proteinuria reduction during this period (19). Therapeutic approaches to iMN mostly relies on steroids and cytotoxics with or without calcineurin inhibitors (20). Rituximab, a monoclonal antibody to CD20 antigen of B cells offers a new therapeutic approach. It safely and persistently reduced proteinuria in a group of patients with iMN who had previously failed to respond to steroids, alkylating agents, or calcineurin inhibitors, or who experienced the relapse after transient remission (21-23). It is also proposed that rituximab reduces the proteinuria by an immune-independent mechanism by targeting sphingomyelin-phosphodiesterase acid-like3B (SMPDL3b) protein that preserves the podocyte cytoskeleton (24). Majority of studies gave rituximab at a dose of 375 mg/m² (square meter) of body surface once weekly for 4 weeks (22, 25, 26). Fervenza et al. gave 1 g rituximab on days 1 and 15; this regimen was repeated at 6 months if B cells were >15/µL and proteinuria was still in the nephrotic range (21, 26). In a recent report at the end of two years of follow-up, CR and PR was observed in 16 out of 20 (80%) patients with iMN. More than half of these patients had failed previous immunosuppressive therapy (21). It is believed that the time has come to conduct a prospective randomized controlled trial in multiple centers with diverse patient populations to assess the efficacy and long-term benefits of rituximab to be compared with traditional immunosuppressive treatment (27).

4. Conclusions

Great discoveries have been performed and great questions remain to be answered. Up to now pathogenic mechanism and triggers for anti-PLA2-R antibody injury are still unknown. Idiopathic MN might be exhibited as a heterogeneous entity rather than a uniform disease. Autoimmune process could also target other poorly understood glomerular antigens beyond what have been discovered recently. Latest findings about the pathogenic role of cationic BSA raise the possibility that other food antigens might be involved in development of idiopathic membranous nephropathy.

Acknowledgments

The author is thankful to Federica Casiraghi and Marina Noris from Mario–Negri Institute of pharmacological research–Bergamo-Italy for their encouragement and assistance in primary preparation of this paper.

Authors’ Contribution

Mohammadreza Ardalan is the only Author of the article.

Financial Disclosure

No financial support by any institution.

Funding/Support

No funding or support by any person or institution.
References

1. Beck LH, Jr., Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361(1):14-21.

2. Hoxha E, Harendza S, Zahner G, Panzer U, Steinmetz O, Fechner K, et al. An immunofluorescence test for phospholipase-A2 receptor antibodies and its clinical usefulness in patients with membranous glomerulonephritis. Nephrol Dial Transplant. 2011;26(8):2526-32.

3. Murtas C, Ravani P, Ghiggeri GM. New insights into membranous nephropathy: from bench to bedside. Nephrol Dial Transplant. 2011;26(8):2428-30.

4. Debec H, Ronco P. Nephrotic syndrome: A new specific test for idiopathic membranous nephropathy. Nat Rev Nephrol. 2011;7(9):496-8.

5. Qin W, Beck LH, Jr., Zeng C, Chen Z, Li S, Zuo K, et al. Anti-phospholipase A2 receptor antibody in membranous nephropathy. J Am Soc Nephrol. 2011;22(6):1117-23.

6. Hofstra JM, Beck LH, Jr, Beck DM, Wetzel JP, Salant DJ. Anti-phospholipase A receptor antibodies correlate with clinical status in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2011;6(12):2186-91.

7. Debec H, Martin I, Jouanneau C, Daunt G,Mesnard L, Rondeau E, et al. Autoantibodies specific for the phospholipase A2 receptor in recurrent and De Novo membranous nephropathy. Am J Transplant. 2011;11(10):2144-52.

8. Schaloske RH, Dennis EA. The phospholipase A2 superfamily and its group numbering system. Biochim Biophys Acta. 2006;1761(1):1246-59.

9. Nevalainen TJ, Kanchanapangka S, Youngprepakorn P, Webb GJW, Manolis SC, Scott KF. Phospholipase A2 activity of crocodile serum. Amphibio-Reptilia. 2009;30:119-25.

10. Saaril EI, Alho V, Paavilainen V, Nevalainen TJ. Group II PLA2 content of tears in normal subjects. Invest Ophthalmol Vis Sci. 2001;42(2):318-20.

11. Fry BG, Vidal N, Norman JA, Vonk FJ, Scheib H, Ramjan SF, et al. Early evolution of the venom system in lizards and snakes. Nature. 2006;443(7105):584-8.

12. Lin MK, Farewell V, Vadas P, Bookman AA, Keystone EC, Pruzanski W. Secretory phospholipase A2 as an index of disease activity in rheumatoid arthritis. Prospective double blind study of 212 patients. J Rheumatol. 1996;23(7):1162-6.

13. Granata F, Petraro Li, Bouard E, Bezzine S, Bollinger J, Del Vecchio L, et al. Activation of cytokine production by secreted phospholipase A2 in human lung macrophages expressing the M-type receptor. J Immunol. 2005;174(4):464-74.

14. Cybulsky AV, Quigg RJ, Salant DJ. Experimental membranous nephropathy redux. Am J Physiol Renal Physiol. 2005;289(4):F660-71.

15. Debec H, Guigonis V, Mougenot B, Decobert F, Haymann JP, Bensman A, et al. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. N Engl J Med. 2002;346(26):2053-60.

16. Debec H, Nauta J, Coulet F, van der Burg M, Guigonis V, Schurmanns T, et al. Role of truncating mutations in MME gene in fe‐tomaternal alloimmunisation and antenatal glomerulopathies. Lancet. 2004;364(9441):1252-9.

17. Makker SP, Tramontano A. Idiopathic membranous nephropathy: an autoimmune disease. Semin Nephrol. 2011;31(4):333-40.

18. Debec H, Lefeu F, Kemper MJ, Niaudet P, Deschenes G, Remuzzi G, et al. Early-childhood membranous nephropathy due to cationic bovine serum albumin. N Engl J Med. 2011;364(22):2100-10.

19. Polanco N, Gutierrez E, Covarsi A, Aitta F, Carrero A, Vigil A, et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. J Am Soc Nephrol. 2010;21(4):697-704.

20. Cravedi P, Ruggenenti P. Circulating anti-PLA2R autoantibodies to monitor immunological activity in membranous nephropathy. J Am Soc Nephrol. 2011;22(8):1400-2.

21. Fervenza FC, Abraham RS, Erickson SB, Irrazabal MV, Eirin A, Specks U, et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. Clin J Am Soc Nephrol. 2010;5(12):2188-98.

22. Remuzzi G, Chiurchiu C, Abbate M, Brusegan V, Bontempelli M, Ruggenenti P. Rituximab for idiopathic membranous nephropathy. Lancet. 2002;360(9337):923-4.

23. Cravedi P, Sghirlanzoni MC, Marasa M, Salerno A, Remuzzi G, Ruggenenti P. Efficacy and safety of rituximab second-line therapy for membranous nephropathy: a prospective, matched-cohort study. Am J Nephrol. 2011;33(5):468-86.

24. Fornoni A, Sageshima S, Mauth J, Weischer-Gomez S, Aguillon-Prada R, Jaureguian AN, et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. Sci Transl Med. 2011;3(85):38ra46.

25. Ruggenenti P, Cravedi P, Sghirlanzoni MC, Gagliardini E, Conti S, Gaspari F, et al. Effects of rituximab on morplofunctional abnormalities of membranous glomerulopathy. Clin J Am Soc Nephrol. 2008;3(6):1652-9.

26. Sprangers B, Lejkowitz GI, Cohen SD, Stokes MB, Valeri A, Appel GB, et al. Beneficial effect of rituximab in the treatment of recurrent idiopathic membranous nephropathy after kidney transplantation. Clin J Am Soc Nephrol. 2010;5(5):790-7.

27. Bomback AS, Dersch BA, McGregor JC, Kharsagar AV, Falk RJ, Nachman PH. Rituximab therapy for membranous nephropathy: a systematic review. Clin J Am Soc Nephrol. 2009;4(4):734-44.