# Membranous Nephropathy in IgG4-Related Disease

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IgG4-related disease (IgG4-RD) is a recently recognized clinical entity characterized by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells with fibrosis affecting several organs.[1] Given the highly variable composition of the disorders comprising the IgG4-RD,[2] only a few epidemiological studies have been carried out into IgG4-RD.[3] IgG4-RD occurs most commonly in middle-aged and older men. This is certainly established for conditions such as IgG4-related autoimmune pancreatitis in which men are affected 3.5 times more often than women. This sex distribution is also recurring in retroperitoneal fibrosis, and IgG4-related tubulointerstitial nephritis (TIN). On the other hand, males and females appear to be affected equally in IgG4-related sialadenitis and IgG4-related ophthalmic disease.[4-6]

Beyond this epidemiological variability, the kidney is one of the most frequently affected organs in IgG4-RD in which TIN is the most representative disorder although a variety of glomerular lesions can sometimes overlap with TIN, such as membranous nephropathy (MN).[7,8] Given the non-unifying nature of IgG4-RD, the diagnostic approach is complex and relies on the coexistence of various clinical, laboratory, and histopathological findings that are sometimes non-pathognomonic of the disease itself.[9] High serum IgG4 level and high IgG4/IgG ratio, histological features of MN confirmed by electron microscopy, and identification of interstitial fibrosis and dense infiltration of IgG4 positive plasma cells, represent the main clinical criteria for the diagnosis of MN associated with IgG4-RD. Despite these distinctive clinic pathological features, the pathogenesis of MN in IgG4-RD remains poorly understood. Autoimmune disease, infections, neoplasms and drugs are the main etiologic factors for the development of secondary MN and, recently, several evidence suggested that IgG4-RD is another systemic disease that can be considered a trigger for the onset of secondary MN.[10,11] Awareness of this rare condition and accumulation of more cases worldwide are mandatory to shed light on the mechanism underlying the development of the disease. Clinical observations in a rare disorder, followed by focused scientific research, often result in the elucidation of both the basic tenets of the mechanisms underlying the MN phenotype and variability.

From the discovery of the immune system potential role in the onset of MN more than 50 years ago, the pathological processes leading to MN has drawn the interest of clinical and experimental investigation.[12] Extensive research in the last decades and spectacular advances in the pathophysiology of the disease, however, have not translated so far into

effective targeted treatments. The glucocorticoids are the standard initial treatment for IgG4-RD, but their long-term adverse effects and the high frequency of relapse have set the urge to identify more effective therapeutic options. Recently, with the discovery of multiple antibodies against specific podocyte antigens in 80% of patients with primary MN, clinical and experimental research as well as patient management have better adapted to the pathophysiology of the disease.[13,14]

The finding that the circulating antibody binding to specific podocyte antigen resulted in the formation of in-situ glomerular immune complex ultimately leading to the development of MN, opened new avenue of interest to unravel the mechanisms by which these circulating antibodies could lead to sub-epithelial immune complex formation in humans.[15] The identification of PLA2R as the target antigen in 70% of patients with MN represented the milestone discovery in the pathophysiology of MN where circulating PLA2R antibodies were able to induce the immune deposit formation and the development of the disease by binding to the PLA2R antigen in podocyte. This finding, however, left the open question on why the 30% of the remaining patients developed MN despite they were negative for PLA2R autoantibodies. The discovery that some of these patients had circulating autoantibodies against THSD7A in a mutually exclusive way with PLA2R antibodies, clearly demonstrated that more than one podocyte antigen could exist and it is now generally acknowledged that MN may have different pathogenic backgrounds in each individual patient.14 In this regard, we recently elucidate the possible mechanism for the development of MN in a subset of patients with IgG4-RD.[16] The majority of patients with IgG4-RD, particularly when associated with autoimmune pancreatitis, have circulating IgG4 subclass antibodies that recognize carbonic anhydrase II (CAII).[17,18] The IgG4-RD patient that we recently described16 does indeed have both circulating IgG4 reacting to CAII and develops MN. Finding that CAII strongly colocalizes with podocalyxin in both controls' and patient's glomeruli, can be taken to indicate that human podocyte, like pancreatic cells, constitutively express CAII. This is an original finding since, to our knowledge, it has never been described before.[16,19] Additionally, the co-localization of CAII and IgG4 deposited in the glomeruli of our patient indicates that CAII is present in the subepithelial immune deposits. This observation indicates that IgG4 anti-CAII antibodies could be responsible for initiating the disease, suggesting a direct relationship between IgG4-RD and MN, which are not merely coincidental. Remarkably, in all IgG4-related disease patients described to date, CAII antibodies were mutually exclusive with PLA2R antibodies, like the THSD7A antibodies in idiopathic MN patients, which would be entirely consistent with the possibility that CAII acts as a primary target in podocytes at least in our patient.[13,14,17,18] Through in vitro studies, we demonstrated the hypothesis of a two-stage model in which IgG4 binding to CAII is critical for altering pH homoeostasis, mitochondrial dynamics, and externalization of mitochondrial enzyme superoxide dismutase 2 (SOD2) on the podocyte plasma membrane. At a later stage mislocated SOD2 serves as a neoantigen for the binding of IgG3-subtype auto-antibodies that is capable of fixing complement and amplifying podocyte injury, contributing to the MN lesion likely favoured by individual genetic predisposition. Indeed, we found circulating IgG3 anti-SOD2 in the patient's serum and IgG3 was the predominant IgG subtype within our patient's glomerular deposits.[20] Although SOD2 has been suggested as a possible neoantigen in non-PLA2R associated MN, it is not clear whether or not the anti-SOD2 antibodies could worsen the existing disease or be informative of its immunologic duration.[21,22] This is a critical issue for the patient care, because the identification of possible biomarker, such as

SOD2, could be a predictable tool for diagnosing and screening of the disease. To confirm such hypothesis future studies will be needed to show that circulating antibodies against SOD2 are in fact present and persist in patients with MN and how they relate to disease activity over time. This would lead to advances in the pathophysiology of MN and to the identification of possible tailored treatment options that are currently lacking.

## References

1. Della-Torre E., Lanzillotta M., Doglioni C. Immunology of IgG4-related disease. Clin Exp Immunol 2015; 181: 191-206.

2. Stone JH., Zen Y., Deshpande V. IgG4-related disease. N Engl J Med 2012; 366: 539-551.

3. Nirula A., Glaser SM., Kalled SL., Taylor FR. What is IgG4? A review of the biology of a unique immunoglobulin subtype. Curr Opin Rheumatol 2011; 23: 119-124.

4. Khosroshahi A, Stone JH (2011) A clinical overview of IgG4-related systemic disease. Curr Opin Rheumatol 23: 57-66.

5. Masaki Y., Dong L., Kurose N., Kitagawa K., Morikawa Y., et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. Ann Rheum Dis 2009; 68:1310-1315.

6. Zen Y., Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol 2010; 34: 1812-1819.

7. Cortazar FB., Stone JH. IgG4-related disease and the kidney. Nat Rev Nephrol 2015.

8. Saeki T., Kawano M. IgG4-related kidney disease. Kidney Int 2014; 85: 251-257.

9. Islam AD., Selmi C., Datta-Mitra A., Sonu R., Chen M., et al. The changing faces of IgG4-related disease: Clinical manifestations and pathogenesis. Autoimmun Rev 2015; 14: 914-922.

10. Nishi S., Imai N., Yoshita K., Ito Y., Ueno M., et al. Ultrastructural studies of IgG4-related kidney disease. Intern Med 2015; 54: 147-153.

11. Alexander MP., Larsen CP., Gibson IW., Nasr SH., Sethi S., et al. Membranous glomerulonephritis is a manifestation of IgG4-related disease. Kidney Int 2013; 83: 455-462.

12. Mellors RC., Ortega LG., Holman HR. Role of gamma globulins in pathogenesis of renal lesions in systemic lupus erythematosus and chronic membranous glomerulonephritis, with an observation on the lupus erythematosus cell reaction. J Exp Med 1957; 106: 191-202.

13. Beck LH., Bonegio RG., Lambeau G., Beck DM., Powell DW., et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009; 361: 11-21.

14. Tomas NM., Beck LH., Meyer-Schwesinger C., Seitz-Polski B., Ma H., et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med 2014; 371: 2277-2287.

15. Debiec H., Guigonis V., Mougenot B., Decobert F., Haymann JP., et al. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. N Engl J Med 2002; 346: 2053-2060.

16. Buelli S., Perico L., Galbusera M., Abbate M., Morigi M., et al. Mitochondrial-dependent Autoimmunity in Membranous Nephropathy of IgG4-related Disease. EBioMedicine 2015; 2: 456-466.

17. Aparisi L., Farre A., Gomez-Cambronero L., Martinez J., De Las Heras G., et al. Antibodies to carbonic anhydrase and IgG4 levels in idiopathic chronic pancreatitis: relevance for diagnosis of autoimmune pancreatitis. Gut 2005; 54: 703-709.

18. Pertovaara M., Bootorabi F., Kuuslahti M., Pasternack A., Parkkila S. Novel carbonic anhydrase autoantibodies and renal manifestations in patients with primary Sjogren's syndrome. Rheumatology (Oxford) 2011; 50:1453-1457.

19. Inada A., Nienaber C., Fonseca S., Bonner-Weir S. Timing and expression pattern of carbonic anhydrase II in pancreas. Dev Dyn 2006; 235: 1571-1577.

20. Cravedi P., Abbate M., Gagliardini E., Galbusera M., Buelli S., et al. Membranous nephropathy associated with IgG4-related disease. Am J Kidney Dis 2011; 58: 272-275.

21. Prunotto M., Carnevali ML., Candiano G., Murtas C., Bruschi M., et al. Autoimmunity in membranous nephropathy targets aldose reductase and SOD2. J Am Soc Nephrol 2001; 21: 507-519.

22. Beck LH., Salant DJ. Membranous nephropathy: from models to man. J Clin Invest 2014; 124: 2307-2314.